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URTICARIA AND ANGIOEDEMA

Statistical Survey of Five Hundred Cases

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THOUGH the urticarial lesion is clearly apparent to patient and physician, the means of its production is not clearly understood. The varied morphology of urticaria, its evanescent character, as well as its multiple causative factors, make accurate evaluation of this condition a rigid task. The advent of antihistamine and hormonal therapy has made urticaria more amenable to treatment, but it has not clarified the etiology or explained the mechanisms involved.

Urticaria as an allergic manifestation was first noted in 1906 by Wolff-Eisner. It is generally accepted that histamine, or an H-substance, liberated at the affected site causes dilatation and increased permeability of the capillaries resulting in wheal formation.[29] When the arterioles as well as the capillaries become dilated to involve tissue over a larger area, particularly a mucocutaneous junction, the phenomenon of angioedema is observed.

Histamine release, subsequent to antigen-antibody union, cannot explain adequately all forms of urticaria. The idea of cholinergic urticaria as mediated by parasympathetic stimulation (acetylcholine as well as mecholyl or pilocarpine) has recently been suggested.[22,24,42] Urticaria in a patient having no demonstrable serum antibodies might be explained, according to this concept, as due to the effect of acetylcholine on the larger arterioles causing increased dilatation and permeability. Whether cholinergic stimulation acts directly on the arterioles or indirectly effects the liberation of histamine is not clear.[42] It is useful, however, to think of urticaria as being of the histamine, or allergic type, and the cholinergic, or non-allergic group.

In order to gain more insight into the genesis of the urticarial wheal, an attempt has been made to evaluate the clinical data of five hundred

unselected case records of urticaria seen at the University Hospital, Ann Arbor, Michigan. The period of study covers twelve years, 1942 to 1953 inclusive. This period is arbitrarily divided into two categories, the first being a study of three hundred case histories from 1942 to 1947, the

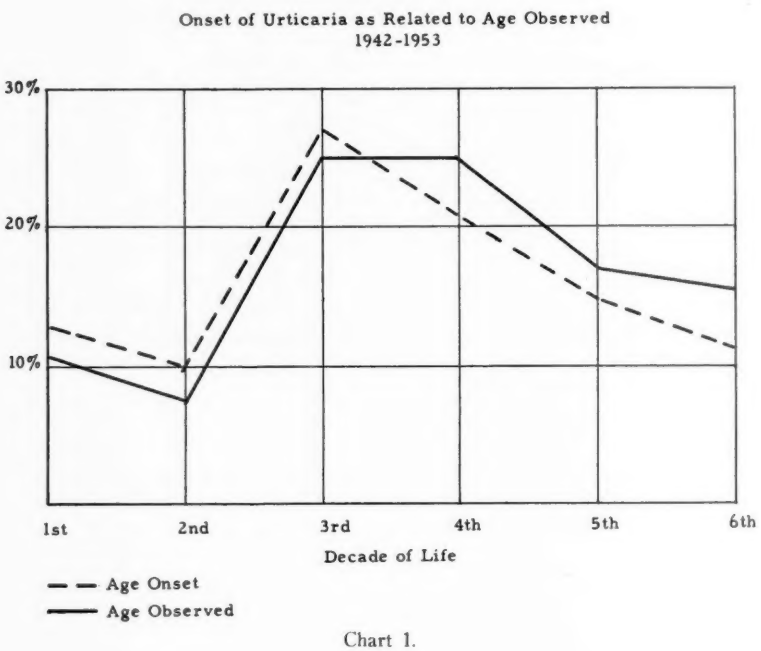

Chart 1.

second a study of a group of two hundred similar cases seen from 1948 to 1953.

The urticarial patients were seen by many examiners in various departments and sections at the University Hospital; therefore, it must be realized that in tabulating the etiologic basis of chronic urticaria only the examiners' clinical impressions were recorded, and verification was not always possible. This applied particularly to out-patients who were observed for a shorter period of time. In general, 117 (23 per cent) were observed from six weeks to several years, while 154 cases (30 per cent) were investigated over a period of from one to six weeks.

Pertinent data are presented in Table I.

As shown, less than two per cent of the patients were of the Negro or Mongolian race. This ratio approximates the hospital census, though no breakdown for this specific period of study was available. Women pre-

dominated somewhat in this study, but perhaps for local factors the variation cannot be regarded as statistically significant. There are, however, several observations recording an increased incidence of urticaria in women.[6,33]

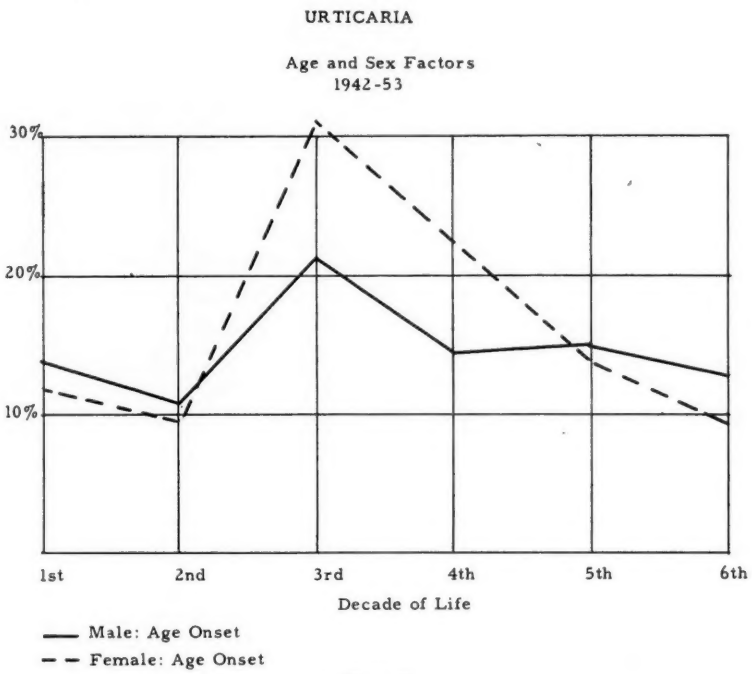

Chart 2.

TABLE I. URTICARIA—RACE AND SEX
1942-1953

A.	Caucasian race	487
	Mongolian race	4
	Negro race	9
		500 cases
B.	Male Sex	235
	Female sex	265

Charts 1 and 2 show an increased incidence of urticaria in the third and fourth decades of life, particularly in females. As may be noted, the age of onset of urticaria closely parallels the period when the patient was seen at the University Hospital. One may possibly explain the greater incidence of urticaria in the second, third and fourth decades on the basis of increased stress situations placed upon the individual during this age period.[22,58]

TABLE II. URTICARIA—ALLERGIC HISTORY

	1942-47 300 cases	1948-53 200 cases
A. Family history recorded	200	143
Positive family atopic history	39%	23%
B. Personal history recorded	252	181
Positive personal atopic history	48%	39%

It is of interest that out of five hundred cases, 119 (31 per cent) showed a positive family history of asthma, hay fever or atopic eczema. Similarly, a positive personal atopic history was recorded in 194 cases, or 43.5 per cent. The decrease in both the family and personal history of associated asthma, hay fever or atopic eczema in the 1948-53 group may be attributed to the fivefold increase of serum-sickness urticaria related to the administration of penicillin during the same period (Table II). Such a preponderance of serum sickness would lower significantly the percentage of positive atopic histories and account for the reduction noted.[37,46,56]

TABLE III. URTICARIA—INTRADERMAL ALLERGENIC TESTS TO COMMON FOODS AND INHALANTS

	1942-53 500 cases
Number of Patients skin tested	256
Per cent of patients tested with significant positive skin test reactions	59
Per cent of total group studied (500 patients) in whom skin tests, when done, showed significant positive skin test reactions	30
Per cent of significant positive skin test reactions in 100 selected cases with positive atopic history (1942-53)	74

A consideration of the results of skin testing in patients (Table III) shows that of 500 cases, 256 were considered worth being subjected by their physician to intradermal allergenic testing for foods or inhalants. Of those patients tested, 59 per cent demonstrated positive reactions which were regarded as significant. When applied against the whole group of 500 patients, this figure suggests that skin testing was felt to be indicated in only about one-half the cases. Results of such tests were actually significantly positive, and therefore perhaps helpful in establishing the etiology in only 30 per cent of the 500 cases.[17,47,52]

Admittedly, had more of the entire group been tested, a somewhat higher percentage of positive skin reactions might have been obtained. But this confirms the writer's experience that skin tests are not indispensable in the search for the etiological agent in urticaria. The history as related to ingestion of foods, drugs, the presence of infection, and evaluation of emotional stress and strain is of paramount importance. In selected cases, however, skin tests may form an important link in the chain of the allergic investigation.

Those with a positive atopic family or personal history, when singled out and evaluated separately, showed a higher incidence of significant positive skin test reactions (74 per cent). This is of interest when compared with

the figure of only 59 per cent significant positive skin tests obtained for all patients tested regardless of atopic history.

TABLE IV. URTICARIA—ETIOLOGICAL FACTORS

	1942-47 300 cases Per cent	1948-53 200 cases Per cent
1. Food		
Primary	18.3	15.0
Suspected or probable	14.0	14.5
Total	32.3	29.5
2. Drugs—Total	17.0	32.5
Penicillin	3.3	15.0
Aspirin	5.3	8.0
Sulfonamides	4.3	.5
3. Psychogenic factors		
Primary	9.6	23.5
Suspected or probable	5.3	16.0
Total	15.0	39.5
4. Infection (Related to onset and duration of urticaria, such as: teeth, prostate, sinuses, appendix, gall bladder)	14.0	14.5
5. Physical and contact allergy (Cold, sun, exercise)	3.3	10.5
6. Undetermined and doubtful etiology (inhalants, endocrine, inoculation, insect bites, serum, toxic, x-ray)	38.3	14.5

One of the most revealing findings in the survey concerns the study of etiological factors (Table IV). Stokes and Pillsbury[49] pointed out in 1935 that urticaria is a "disease of complex rather than single causation." An etiologic agent, by itself incapable of causing an urticarial reaction, may by interplay with other factors permit a sum-total clinical effect. A patient may experience hives by reacting to strawberries only during the ragweed season, or he may experience urticaria as a result of a particular food or drug only during a state of nervous tension and fatigue, or during menstruation when the allergic equilibrium or load is altered. Disturbance in gastrointestinal absorption may also predispose to increased allergic manifestation.

This multiphasic aspect of urticaria can best be illustrated when one is treating an infection with penicillin, sedatives and aspirin. The physician is confronted with the question whether the resultant urticaria is due to the infection or to the medications used. Similarly, under given circumstances of urticaria produced by a food, one may ask if the reaction is entirely due to an allergic mechanism or whether the food evokes in the patient some type of emotionally-charged experience which acts as a psychic trigger in potentiating the reaction. This latter mechanism might explain why an adult, forced to drink milk as a child by an overbearing parent, may have urticaria from ingesting a glass of milk, but may be symptom free when milk is fed in disguised forms.[19,44,49]

From study of Table IV it can be noted that food allergy was suspected in 30 per cent of the diagnosed cases of chronic hives. Only those patients who were improved by the removal of the suspected food were classified as primary food urticaria. This group comprised 18.3 per cent of cases prior to 1948, and 15 per cent of those seen thereafter. The instances where

food was suspected but not fully corroborated were classified as probable (14 per cent). Analysis of the specific foods incriminated showed that it was not always the unusual, but rather the common everyday staple foods which were most often the cause of symptoms.

The nearly doubled incidence (32 per cent) of drugs, acting as urticariogenic agents in the recent period could most likely be attributed to the fivefold increased use of penicillin, and to the common use of aspirin.[43] The concomitant decreased use of the sulfonamides during the same six-year period was insufficient to offset the greater frequency of penicillin reactions.

The high number of cases of urticaria during the 1948-53 period which were attributed to psychological factors (39.5 per cent) is probably due to a greater emphasis placed on a more careful evaluation of the emotional status of the patient as compared to the early years (15 per cent). In the classification of psychogenic urticaria, the presence of a neurotic element in the patient's personality was not considered adequate basis for placing him in the psychogenic group. If, however, the tension and emotional conflict occupied a central part of the symptomatology and were related in timing, then the psychic factors were regarded as primary. The studies of Graham and Wolf[22] and others have drawn attention to the tremendous importance of emotional factors in the genesis of the urticarial lesion. They concluded that the dilatation of the arterioles and capillaries of the skin is initiated by stressful life situations, particularly those in which feelings of resentment and helplessness are involved.

Urticaria associated with infection was recorded in seventy-one cases. The 14 per cent of cases so represented included various types of infection such as cholecystitis, appendicitis, infected teeth or tonsils, chronic prostatitis, cutaneous infection, and parasitic infestation. In each case the examining physician considered the evidence of infection strong enough to chart it as the basis for the urticaria.

Physical allergy[1,11,13,23,57] as represented by exercise, sun, or cold urticaria has increased in the last six-year period. This possibly may be attributed to a greater awareness of this phenomenon by the hospital staff.

Contact urticaria, caused by direct handling of wool, cats, dogs, and mice by laboratory workers was found in seven cases from each study period.

As to urticaria of undetermined or questionable etiology, the following may be listed:

1. *Inhalants*[48]—particularly urticaria due to pollen occurring during the season and responding to specific hyposensitization. Most of the patients had associated hay fever and/or asthma.

2. *Endocrine*—including urticaria related to pregnancy, menopause, thyroid, or insulin injections.

3. *Inoculation and insect bites*[2,3]—in this group are found several cases of urticaria accompanying scabies.

4. *Miscellaneous*—urticarial reactions to x-ray therapy and "toxic urticaria" (specific agent undetermined).

After enumerating the above factors, the reviewer still was confronted with a variable number of urticarial patients who defied all attempts at analysis, and were therefore classified as "etiology undetermined."

The sharp decrease in this heterogeneous undetermined group during recent years, with the concomitant doubling of the psychogenic urticaria, may perhaps be related to the more prevalent evaluation of the psychophysiologic factors in urticaria. This fact would tend to reduce the number of cases classified as undetermined.

MORPHOLOGY AND EOSINOPHILIA IN ETIOLOGIC STUDY

The morphology of the urticarial lesions was studied and characteristics noted. Out of five hundred cases reviewed, angioedema occurred in two hundred sixteen patients during the course of urticaria. The incidence has increased from 35 per cent in the first six-year study to 54 per cent in the second six-year period. This too, would appear to be related to the more prevalent penicillin serum sickness in which angioedema and urticaria usually occur simultaneously. In over one-half of the cases recorded, the predominant location of the angioedema was described as present on the face, lips, eyelids, and throat. A predilection of angioedema for mucocutaneous junctions was seen.[47]

Fifteen patients with erythema multiforme showed urticarial lesions. It has been suggested by Sheldon, Lovell, Mathews, Curtis et al[47] that certain etiological agents such as food, drugs, infections, and tension may influence the morphological characteristics such as size, shape, color, duration, and distribution of the urticarial lesion. That clinical impression was corroborated in this series by many examiners. It may be stated that the number of cases with complete morphological data in this series was not considered adequate to draw definite conclusions.

Blood eosinophilia as recorded in fifty patients was found to be of no diagnostic help. More than one-half had no eosinophils, while the remainder showed only slight eosinophilia.

The therapeutic approach was diverse and consisted principally of the following: (a) elimination of the causative factor, (b) dietary, (c) hormonal, (d) drug, (e) non-specific, (f) local, (g) immunologic, and (h) psychotherapeutic measures. There were forty-two patients, 7.6 per cent, whose lesions or symptoms were mild and who spontaneously recovered before therapy was instituted. Complete recovery by elimination of the specific causative factor such as a food, a medication, or a contact was accomplished in thirty-eight instances (7.5 per cent). This obviously is the most definitive type of therapy.

Elimination diets and food restriction was carried out in 174 cases.

Food factors as causative agents could be conclusively demonstrated in only eighty-five cases.

TABLE V. URTICARIA—TREATMENT

	1942-47 300 cases Per cent	1948-53 200 cases Per cent
1. None required (mild, spontaneous remission)	11.3	4.0
2. Elimination of causative agent (no other treatment)	8.0	7.0
3. Diet manipulations (investigative)	36.6	32.0
4. Hormonal therapy (ACTH and Cortisone)	0	8.0
5. Drugs		
a. Antihistamines	28.3	64.5
b. Vasodilators: Aminophyllin and Nicotinic Acid	2.3	10.0
c. Antibiotics: Penicillin, Aureomycin, Terramycin	0	4.7
d. Sulphonamides	3.0	.5
e. Ephedrine and Adrenalin	8.3	5.0
f. Tonics and Alteratives (KI, Calcium, Acid Phosphate)	10.3	1.5
6. Non-Specific Therapy—Histamine (Hapamin), Liver, Vaccine	10.0	1.0
7. Miscellaneous:		
a. Decreasing Temp. baths, Amm. Chloride, Endocrine products, Lactic Acid (3 cases in 1948-53), Procaine I.V. (4 cases)	2.0	4.0
b. Hyposensitization to Inhalants	3.3	10.0
8. Local Therapy (Calamine and Colloidal Baths)	7.6	4.5
9. Psychotherapy—Intensive	2.6	5.5

Hormonal therapy (ACTH and Cortisone) was employed during the last four years in sixteen patients with serum sickness due to penicillin. Remissions of urticaria occurred in all instances within twenty-four to seventy-two hours. It is interesting to note that two out of sixteen had reactions (allergic?) after ACTH administration.

Antihistamines, particularly Pyribenzamine® and Benedryl® were used in eighty-five cases (28.3 per cent) in the first group during 1942-47, while in the more recent group various antihistamines were employed in 129 cases.[10] It may be noted that the high percentage, 78 per cent, of clinical improvement in patients evaluated could be attributed to the effect of the antihistamines.

Vasodilators, represented by aminophyllin and nicotinic acid, were used in 2.3 per cent of the 1942-47 group as compared with 10 per cent in the 1948-53 cases. The results of nicotinic acid appeared to be beneficial, but in many instances other forms of therapy were employed simultaneously.[46]

Antibiotics were used in nine cases during the latter period, while sulfonamides were used only in one instance in the recent six years. During the 1948-53 period it is interesting to observe that one-third of the urticaria cases associated with infection were treated with antibiotics. In erythema multiforme with predominant urticarial lesions therapy also was directed against the infection, though the urticaria was presumed to be allergic in origin.

Ephedrine and epinephrine were administered in 8.3 per cent of the early group as compared to 5 per cent of the later group. All experienced some degree of temporary improvement.

Tonics and alteratives: (a) Potassium iodide, calcium gluconate, and phosphates were employed in 1.5 per cent of the recent cases as compared to 1.3 per cent in the earlier group. Intravenously administered calcium appeared to be useful in relieving the pruritus associated with urticaria; (b) Histamine Azo-Protein was tried in thirty instances experimentally during the 1942-47 period. Benefit rarely was recorded; (c) Lactic acid was given hypodermically in three patients who had urticaria after exercise.[23] None of these patients was improved permanently.

Decreasing bath temperature was used in cold allergy with doubtful results.[27] Procaine by slow intravenous drip (1 gm in 500 cc of 5 per cent glucose) was used in four patients. One was improved and three were unimproved.

Local therapy[47,52] such as calamine lotion, wet compresses, and colloidal baths have not been resorted to frequently during the recent six-year period.

Referral to the Neuropsychiatric Department for intensive psychotherapy doubled in the 1948-53 period to 5.5 per cent. This measure was employed in addition to the usual supportive and informal psychotherapy used by the allergist or dermatologist in treatment of patients who were tense and emotionally disturbed. This emphasis on psychotherapy is undoubtedly due to a greater awareness of the important part psychophysiologic factors play in the pathogenesis of many somatic manifestations, particularly that of urticaria.

It is interesting to note that more patients were given sedation in the recent period. In addition to the barbiturates, administration of the antihistamines also must have exerted a sedative effect on many patients.

COMMENTS

A critical analysis of the data presented focuses our attention on some of the problems encountered in this type of study. The following considerations present themselves:

1. Inconstancy of the skin manifestations makes comparison and accurate description of lesions difficult. This may account in part for the paucity of the morphological data recorded.
2. The tendency to spontaneous remissions, and the multiplicity of causative factors frequently strains the validity of the etiologic diagnoses. For example, the disappearance of urticaria following tonsillectomy is not proof that the infected tonsils were the basis of the urticarial reaction.
3. Orientation and training of many examiners greatly affects the accuracy and emphasis in the etiologic diagnoses.
4. Duration of the observation period is quite important in this survey if the conclusions are to be given the proper weight.
5. Thoroughness of the history and general physical examination, the opportunity for referrals, and follow-up are not the least important elements.

In this survey of 500 unselected cases of urticaria a certain unavoidable degree of error is inevitable. But due to the many positive factors and

high standards present at the institution as well as the large number of cases under study, the inaccuracies are relatively small.

The writer would like to suggest the following in order to further reduce error to a minimum degree:

1. A definite minimum observation period should be adopted. A period of three to six months would tend to exclude those who would recover spontaneously.
2. Patients with urticaria, though referred to various departments for consultation, should be the responsibility of one group who will direct all phases of investigation.
3. Certain definite uniform criteria and standards should be set up. Urticaria, suspected of being caused by a food or a medication should not be placed in that etiological category unless the re-introduction of the food or drug produces the same symptoms.
4. Each urticarial reaction when first seen should be described morphologically, such as size, shape, color, duration, etc. Just as one is not content with merely stating that a cardiac lesion exists, so the statement of the presence of an urticarial reaction is not adequate without further description and qualification.
5. Follow-up studies should be carried out to obtain more information as to contributory factors and possible recurrences.
6. Psychologic evaluation is desirable in the complete investigation of the chronic urticarias, as our observations have demonstrated.

CONCLUSIONS

Our survey of 500 cases of urticaria and angioedema is presented as a group encountered in a large medical center. With the reservations stated previously, the following results are summarized as noteworthy:

1. Urticaria is more common in the twenty to forty age group and is particularly noted in females. The increased incidence of urticaria in young women perhaps may be related, in addition to possible psychic trauma, to the prevalent use of medications during the child-bearing age, and to a greater incidence of pelvic infections and endocrine imbalance related to pregnancy and menopause.

2. As in other allergic manifestations, a positive family or personal history is valuable in the diagnostic survey. Those patients with an atopic history showed a greater incidence of significant skin reactions than did the group as a whole.

3. Skin tests appear to be of little help in urticaria and angioedema as far as determining etiology. Neither is the eosinophile count an absolute diagnostic aid. The detailed history remains the cornerstone of the investigation program.

The etiologic factors were appraised statistically, and the difficulties that beset this type of clinical study were pointed out. A recent emphasis on drugs, particularly penicillin and aspirin, as well as the importance of emotion, were clearly seen.

In general, therapy employed, particularly antihistamines, proved effective in relieving the pruritus in 78 per cent of the patients evaluated. Thirteen per cent had complete recovery through removal of the causative factor. Seven per cent did not respond favorably to any of the methods employed.

The temporary use of ACTH[47] and cortisone, especially the former, would appear to be justified in serum sickness of moderate or severe degree.

A search for the etiological factor and its elimination will therefore remain the goal of ideal therapy. However, in order to achieve a greater degree of effectiveness in the treatment of chronic urticaria, the predisposing and emotional factors must be thoroughly considered.

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HISTOPATHOLOGY OF ALLERGIC DERMATOSES

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IN DEALING with the histopathology of allergic dermatoses, I have to make one reservation which can be expressed best by quoting Sulzberger: "In my opinion, there are no organic changes, no tissue alterations . . . which are in and of themselves pathognomonic of allergy . . . almost every reaction . . . based on allergy (can) be produced also by non-allergic mechanisms . . ."[15] Keeping this reservation in mind, my purpose will be to present and analyze the various tissue changes that are produced in the skin by allergic mechanisms, but I shall not claim that these changes are necessarily pathognomonic for allergic disease.

TABLE I. TYPES OF TISSUE REACTION

1. Epidermal
2. Urticarial
   (a) atopic
   (b) erythematous
   (c) vascular
3. Tuberculin Type.

There is a great variety of allergic dermatoses. This is due to the complicated structure of the skin organ, which consists of derivatives of the ectoderm and the mesoderm; of epidermis, hairs, and glands; of connective tissue, blood vessels, smooth muscle, and nerves. It is also due to the specific function of the skin as a protective armor for the body, not only against the onslaught of chemical and infectious agents from the outside, but through its participation in many immunologic processes in systemic disease. For my specific purposes, I have tabulated tissue changes in allergic dermatoses in a manner that expresses morphologic relationship and, by implication, transitions from one morphe to another. This transition actually may be found during the development of one case, or it may be construed by comparing individual cases within the group. Table I is an outline of my presentation, much of which is based on Sulzberger's ideas as he presented them in his book on Dermatologic Allergy.[15]

I shall restrict myself to allergic dermatoses in the classical sense, and shall omit entities like the collagen diseases and others in which the role of allergy and hypersensitivity is being discussed but not proved.

1. *Tissue Reactions Based on Epidermal Response.*—Predominantly epidermal reaction is found in dermatitis caused by external contact

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(Chart 1). The type of reaction is almost identical whether the dermatitis is due to a primary irritant, or to a substance to which the individual has become sensitized.

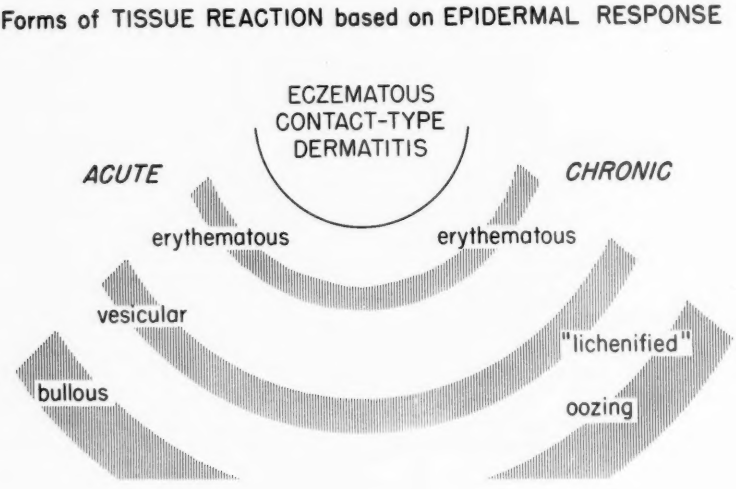


Chart I.

According to general concept, the first visible change in the skin is alteration of individual prickle cells and intercellular edema (Fig. 1), leading to spongiosis and formation of the "primordial vesicle" when the damaged cell is dissolved. Charpy[3] recently described still earlier changes within an hour or two of the application of the noxious substance, and believes that vasodilatation and edema of the corium are primary and lead only secondarily to epidermal edema and to the changes described by Civatte. In this controversy, it may be pertinent to recall the demonstration, by Menkin,[10] of histamine-like and leukotactic substances being liberated from damaged cells, and the recent finding of Wells and Babcock[16] that epidermal cells contain proteolytic enzymes which are easily liberated from damaged cells and may provoke inflammatory changes in the corium. One might theorize that epidermal damage is primary after all, but does not become visible under the microscope before substances liberated from the epidermis have led to vascular reaction in the corium.

At later stages (Fig. 2), contact dermatitis is characterized by epidermal edema which is mostly intercellular and leads to spongiosis. Eventually,

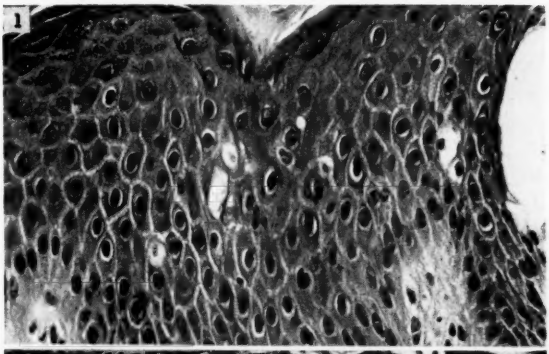


Fig. 1. Alteration cavitaire. Fading of individual prickle cells in the epidermis close to an eczematous vesicle which is visible at the right.

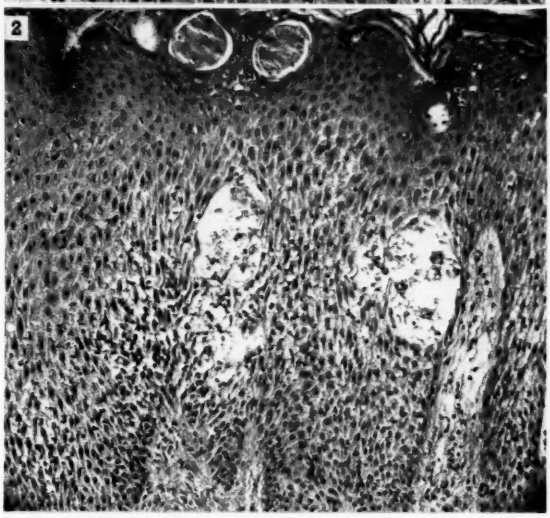


Fig. 2. Epidermis in acute contact dermatitis showing intercellular edema, spongiosis, vesiculation and transmigration of leukocytes (exocytosis).

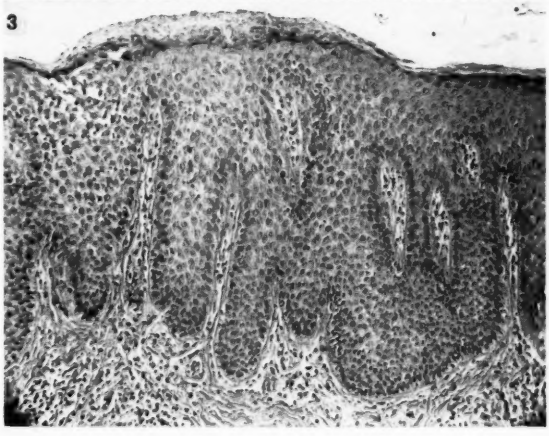


Fig. 3. Chronic contact dermatitis with lichenification. Epidermis exhibits acanthosis, parakeratosis, and occasional areas of spongiosis and exocytosis.

when the overstretched intercellular bridges rupture, intra-epidermal vesicles result. Soon a regenerative effort of the basal cells leads to new formation of cells. The epidermis becomes hyperplastic, and the damaged tissue is gradually pushed outward. The edematous strata undergo an accelerated process of faulty keratinization in which the nuclei do not disappear (parakeratosis). At the same time, inflammatory cells, leukocytes and also lymphocytes, invade the epidermis. All these processes, based on local cell damage as they are, occur in spotty fashion throughout the affected area, and repeat themselves while the irritation continues. Thus all stages of the epidermal alteration can be seen side by side in the same section and form the typical "punctate" picture of eczematous dermatitis. The upper corium, meanwhile, shows edema and perivascular lymphocytic infiltrate around dilated blood capillaries which release swarms of leukocytes into the epidermis. Eosinophils often are present, but usually are not numerous.

The degree of epidermal hypertrophy can be tremendous in acute cases as in Figure 2 which illustrates a dermatitis caused by a drawing ointment, i.e., by a primary irritant. Similar and even worse pictures can be found in bullous poison ivy dermatitis, i.e., in true sensitization. In more chronic cases of contact dermatitis (Fig. 3), the acute, exudative factor is less pronounced, epidermal hyperplasia, so-called acanthosis, becomes more prominent, and finally, assisted by the patient's rubbing and scratching, the state known clinically as "lichenification" is reached, in which acanthosis and hyperkeratosis rule the picture. However, with each new flare of the dermatitis, the typical "eczematous" epidermal changes recur.

2. *Tissue Reactions Based on Urticarial Response.*—The next large group of allergic dermatoses can be thought of as based on the urticarial response (Chart 2). This statement is meant in a purely morphological sense, and does not imply the suggestion that the clinical disease urticaria often develops into the other entities listed. Rather a very early lesion of the more severe dermatoses resembles urticaria, a fact that was pointed out for atopic dermatitis by Sulzberger. The basis of the similarity is of course that all these dermatoses are intimately connected with a vascular reaction, and that in its turn may be due to the fact that in most cases a soluble allergen is brought into the skin by the blood stream. The initial vascular response may develop in different directions. It is the task of the dermatopathologist to interpret and differentiate these pathologic changes from each other, and it is for that reason that I group these dermatoses around the central "urticarial response."

The acute urticarial wheal is characterized by dilatation of capillaries, exudation of fluid through the vascular wall, and accumulation of eosinophils in the perivascular tissue. These changes, as W. Jadassohn[8] has shown, are similar in allergic urticaria and in non-allergic whealing. They appear to be the typical response to histamine and histamine-like substances. From then on, the development of the lesion varies.

A. In atopic dermatitis, we find what Sachs, Miller, and Gray[13] described as the neurodermatitic reaction. In its fully developed form, the epidermis is moderately thickened, acanthotic, with unevenly long rete

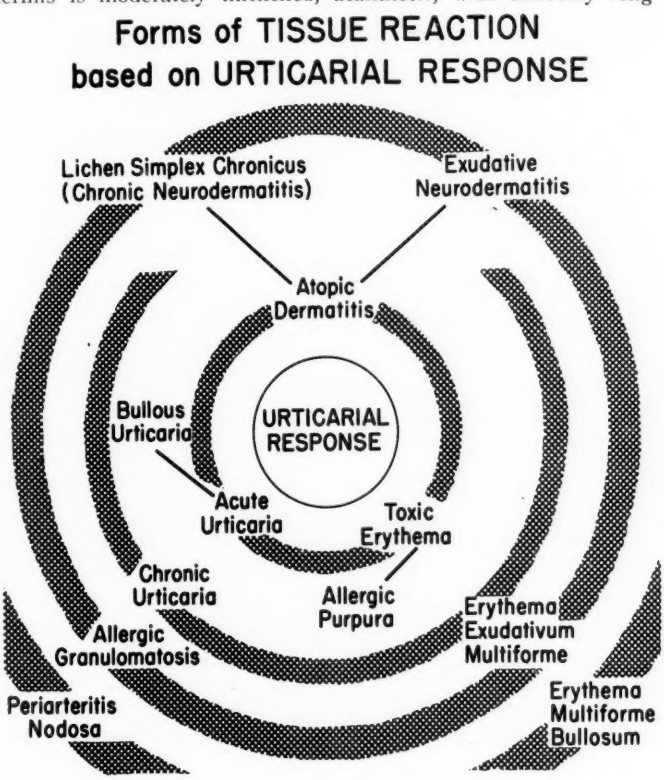


Chart II.

ridges and broad, unevenly shaped papillae. There is spotty parakeratosis, and there may be intraepidermal vesiculation. Exocytosis, i.e., transmigration of leukocytes and lymphocytes into the epidermis, is present. The papillae and subpapillary layer exhibit considerable thickening of the vascular walls due to endothelial swelling and increase of the adventitial cells. There is fairly pronounced, sometimes almost nodular, perivascular infiltrate which consists mainly of lymphocytes but also shows an increase of fixed tissue type cells, probably histiocytes. Eosinophils may be present in varying numbers. Edema of the upper corium varies depending on the phase of the process, and gradually fibrosis is added to the picture. Figure 4 shows a fairly early stage of atopic dermatitis, while Figure 5 illustrates a more chronic quiescent stage. In very chronic stages, the same type of lichenification is seen that is the end result in chronic contact dermatitis (Fig. 6). It should be pointed out that clear-cut

histologic differentiation between chronic contact dermatitis and chronic atopic dermatitis may be very difficult. Only too often, mixed pictures are found because atopic dermatitis usually is complicated by contact factors, and contact dermatitis becomes lichenified due to chronic scratching and irritation.

The presence of fibrosis and of chronic changes of vascular walls are the visible expression of the fact that — just as in asthma in the lung so in atopic dermatitis in the skin — secondary changes develop which are not easily reversible. Just as emphysema and bronchiectasis are not improved by withdrawal of allergens or by desensitization, so tissue changes in the skin cannot be expected to disappear in a few weeks or even months. Fortunately, they are not as irreversible in many cases as are pulmonary changes in bronchial asthma.

B. The next important group of rather characteristic tissue reactions is the toxic erythemas. Early lesions of this type resemble acute urticaria histologically as well as clinically. However, just as the clinical lesion does not wane but progresses for several days through various stages, so histologically more extensive tissue damage and inflammatory response become evident. Edema of the superficial corium becomes pronounced and perivascular lymphocytic infiltrate with or without eosinophils is prominent (Fig. 7). Often the overlying epidermis is edematous in a peculiar way with all the prickle cells elongated perpendicular to the surface of the skin. One gains the impression that an outpouring of fluid from the corium into the intercellular spaces is stopped by the solid barrier of the keratin layer (Fig. 8).

This is the picture that is found in many drug eruptions of maculopapular character. It can progress in two main directions. In those lesions that become purpuric, endothelial swelling with diapedesis of red cells, or even necrosis of capillary endothelium with actual rhexis and hemorrhage, occurs. These changes usually are associated with severe edema and leukocytic infiltrate in the upper corium.

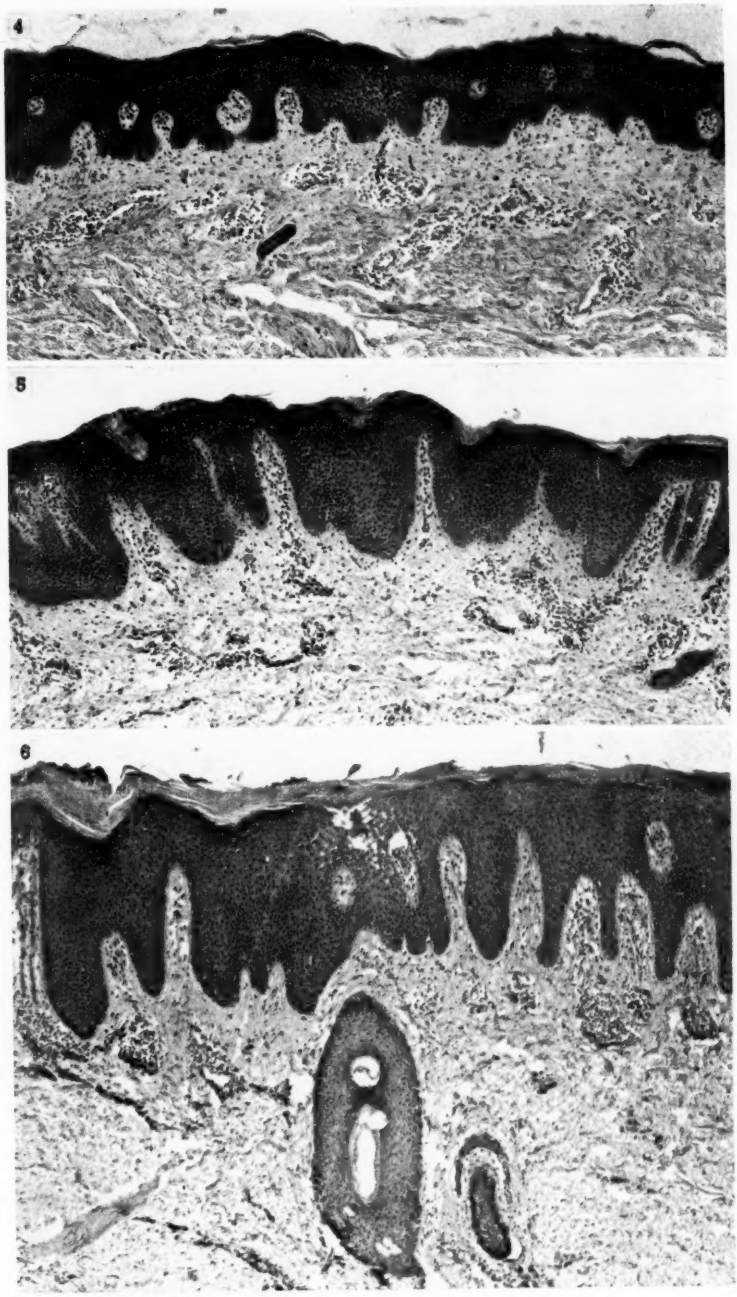
On the other hand, vascular damage may remain limited, but the subepidermal edema may assume almost bullous proportions, and the epidermis may show damage exceeding the passive type of edema. Degeneration of prickle cells and necrosis of whole stretches of the rete may occur. These are the changes found in the toxic-allergic eruptions of erythema

(See opposite page)

Fig. 4. Atopic dermatitis (flexural eczema). Fairly early stage showing some epidermal acanthosis and parakeratosis and a few areas of intercellular edema. The corium shows edema, increased cellularity, and prominent blood vessels with perivascular lymphocytic infiltrate.

Fig. 5. Atopic dermatitis, later stage. More acanthosis, less parakeratosis. Corrugation of epidermal surface is the histologic expression of clinical lichenification. More fibrosis and less infiltrate in the corium.

Fig. 6. Lichen simplex chronicus (circumscribed neurodermatitis) in state of exacerbation. Epidermis highly acanthotic. Left half shows hyperkeratosis and corrugation of the epidermal surface, center shows acute edema and near-vesiculation, right half shows parakeratosis corresponding to subsidence of the acute phase and exfoliation. Corium exhibits strictly perivascular infiltrate, hyperkeratosis of hair follicles and sebaceous atrophy.



exudativum multiforme type. They are accompanied by heavy leukocytic and lymphocytic infiltrate in the entire corium. If bullae develop, they are subepidermal, and the covering epidermis usually is severely damaged, often quite necrotic (Fig. 9). Partial necrosis of the superficial layers of the corium may occur.

C. In some contrast to this type of tissue reaction which becomes more stormy with increasing severity and always runs an acute course, one can construct another graduated series of reactions, again beginning with acute urticaria, but now increasingly chronic, and proliferative rather than exudative in character.

If we examine a case of chronic urticaria (Fig. 10), one with less acute, more papular, lesions which persist for a day or two, rather than only for a few hours, we find a perivascular lymphocytic infiltrate with some swelling of the vascular wall and a scattering of eosinophils in the infiltrate as well as in the intervening tissue spaces.

Then there are more severe nodular reactions of allergic origin, often associated with signs of systemic disease. Such cases have been collected recently by Churg and Strauss[4,14] under the designation of allergic granulomatosis. They may be considered to be more chronic and show more proliferative tissue response to blood-borne allergens. In these cases the early stage of the lesion is characterized by edema and leukocytic exudate around the blood vessels, but the leukocytes soon become necrotic, fibrinoid changes in the collagen set in, and a granulomatous reaction with histiocytes, sometimes in epithelioid arrangement, and with numerous eosinophils develops (Fig. 11).

The most severe reaction of this type is seen in polyarteritis nodosa. According to Ormsby and Montgomery "cutaneous manifestations (in this disease) vary from simple erythema to erythema multiforme or erythema nodosum, urticaria, and even purpura. Subcutaneous nodules develop which occasionally are followed by vesicular, pustular, or necrotic lesions."[11] This quotation nicely emphasizes the relationship between the various manifestations in the "urticarial response" group. The typical tissue reaction (Fig. 12) in the nodules of periarteritis nodosa is a necrotizing arteritis which is localized, sometimes only affects one segment of the vascular wall. There is hyaline or fibrinoid necrosis of the wall with predominantly leukocytic infiltrate which usually contains numerous eosinophils. There may be marked proliferation of the intima, and granulomatous histiocytic infiltrate in the surrounding tissue.

3. *Tissue Reactions Based on Tuberculin Type Response.*—The last large group of allergic tissue responses are those based on the tuberculin

(See opposite page)

Fig. 7. Erythematous purpuric drug eruption illustrating toxic erythema. No definite alterations of the epidermis. Strictly perivascular infiltrate in the corium. Red blood cells in the tissue at the lower border of the picture.

Fig. 8. Typical configuration of epidermal edema in toxic erythema.

Fig. 9. Erythema exudativum multiforme showing partial necrosis of the epidermis, subepidermal bullous edema, partial necrosis of the superficial corium and acute inflammatory infiltrate.

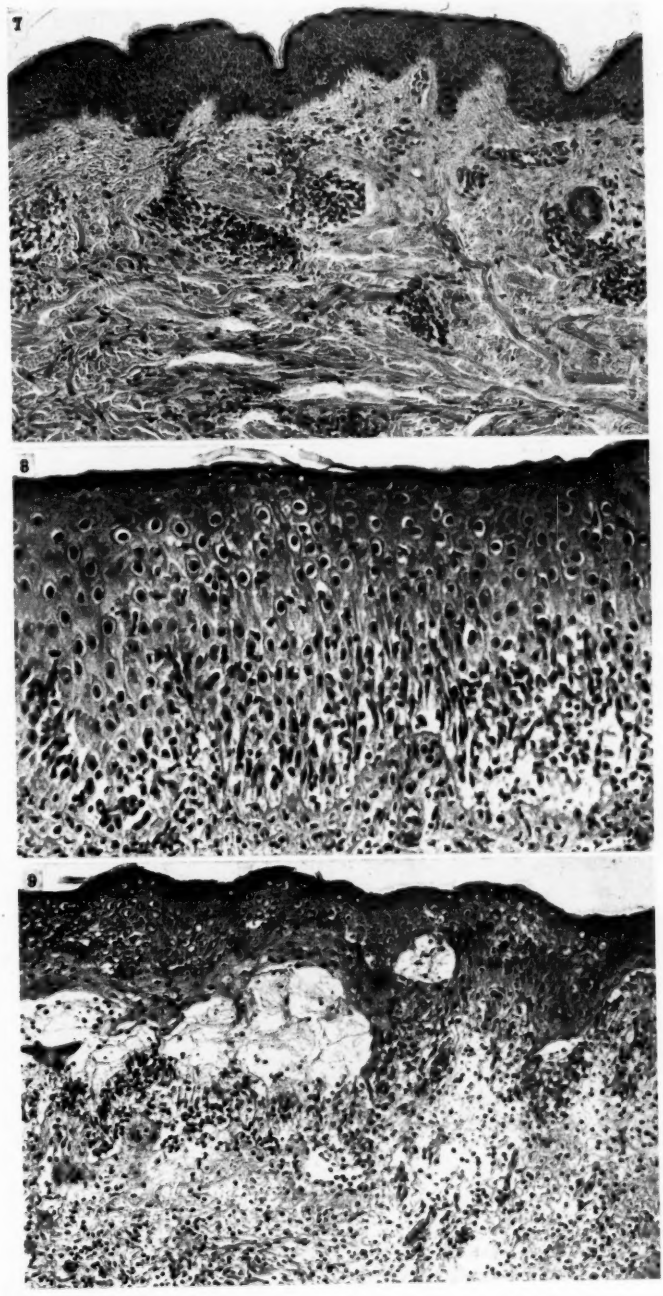


TABLE II. FACTORS DETERMINING CUTANEOUS REACTION TO INFECTION WITH TUBERCLE BACILLI

1. Invader:
   (a) strain (human, bovine, etc.)
   (b) virulence
   (c) number
   (d) viability
2. Host:
   (a) physiologic state (age, etc.)
   (b) general health
   (c) genetic factors (native resistance)
   (d) specific immunity (hypersensitivity, acquired resistance, special mechanisms: anticutins, etc.)
3. Terrain:
   (a) site of localization (region of body, part of skin)
   (b) route of invasion (exogenous, endogenous: by contiguity, lymph stream, bloodstream)

type of allergy, which in most instances corresponds to Sulzberger's allergy of infection. Histopathologists refer to these manifestations as chronic granulomatous inflammation, a term which covers most of the chronic infectious diseases and some non-infectious entities. I shall restrict myself here to the discussion of one of them, the prototype: Tuberculosis. I do not have to go into detail concerning the basic principles of allergic tissue response to the tubercle bacillus. Koch's classic experiment in the guinea pig and Lewandowsky's investigations of the histologic basis of the altered reaction to primary and secondary infection are basic knowledge.

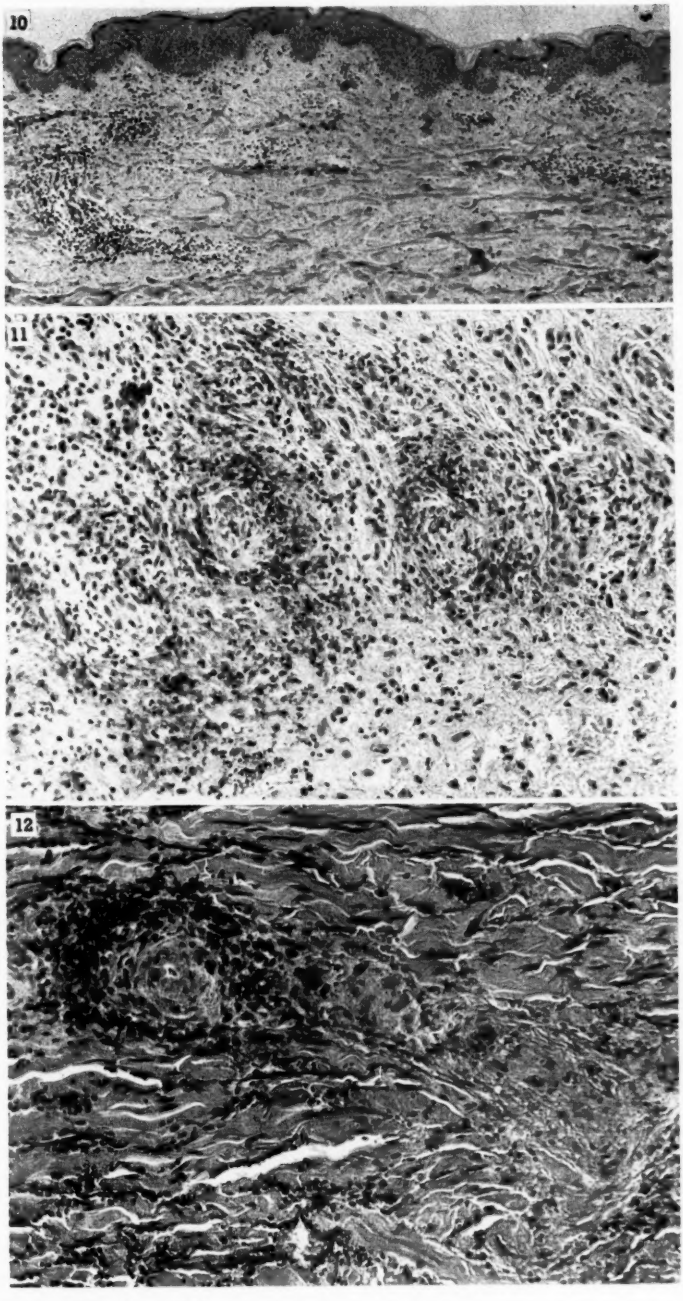
In the human skin, tissue response and, with it, the clinical picture can vary a great deal. They depend on several factors, only one of which is the specific immunologic state of the individual (Table II). The number and virulence of the invading organism, the route by which it reaches the skin, and the exact site at which it localizes, all play their part in determining what will happen. However, one *common* factor, it seems to me, needs stressing. That is the fact that an allergen is deposited in the substance of the skin and remains and acts there for a considerable length of time. This situation is different from contact dermatitis, where a noxious substance acts on the epidermal barrier from the outside, and it is different from "urticarial" allergic dermatoses in which soluble allergens reach the skin via the blood stream. The presence of a relatively insoluble, hard-to-remove allergen within the substance of the corium seems to go far in explaining certain aspects of the tissue response in tuberculin type allergy.

(See opposite page)

Fig. 10. Chronic urticaria. No epidermal changes. Perivascular and scattered infiltrate in the corium. Many of the scattered cells are eosinophils.

Fig. 11. Allergic granulomatosis. Infiltrate is centered around blood vessels which exhibit intimal swelling, but no necrosis. The infiltrate consists of histiocytes, lymphocytes and polymorphonuclears many of which are eosinophils.

Fig. 12. Periarteritis nodosa. A small artery is shown in the deep corium. The left half of the picture shows a cross section with intimal necrosis and dense, predominantly eosinophilic infiltrate around the artery. The right half shows the same artery in longitudinal section and exhibits complete necrosis of the vessel and surrounding infiltrate.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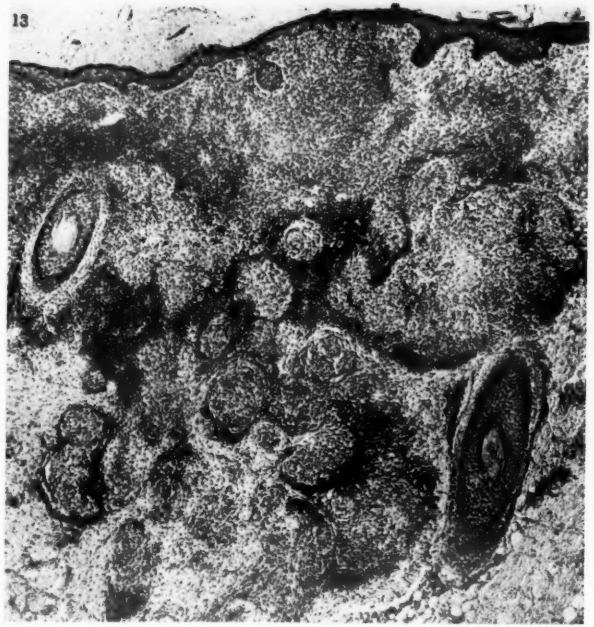

Fig. 13. Tuberculosis luposa (lupus vulgaris). Massive epithelioid cell tubercles surrounded by lymphocytic shells. No necrosis or caseation.

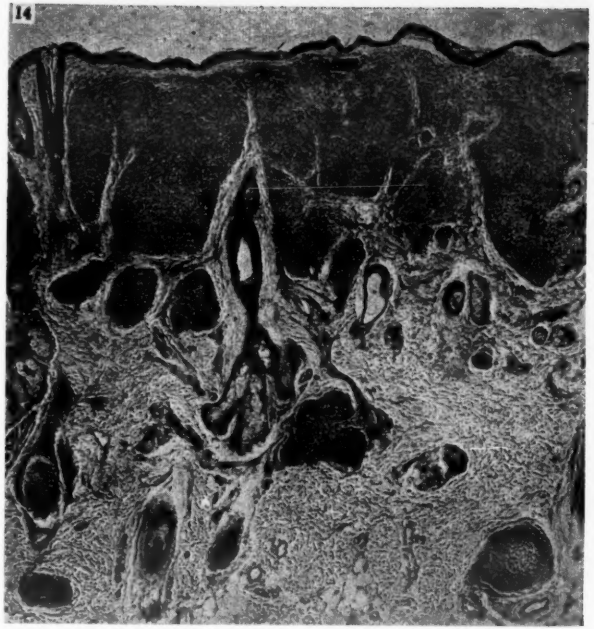

Fig. 14. Sarcoidosis (Boeck's sarcoid). Massive "naked" epithelioid cell tubercles without lymphocytic shells.

TABLE III. FORMS OF TISSUE REACTION BASED ON TUBERCULIN TYPE RESPONSE

(Example: Tuberculosis)	
Progredient:	Self Limited:
Tuberculosis Orificialis	Lichen scrofulosorum
Tuberculosis Luposa (lupus vulgaris)	Papulonecrotic Tuberculid
Sarcoid Reaction	Erythema induratum

Tuberculodermas, according to their prognosis, can be classified as progredient or self limited (Table III). If living tubercle bacilli are implanted into the skin or mucous membranes of an infected and relatively defenseless individual, a progredient ulcer develops, as in tuberculosis orificialis, in which we find numerous bacilli and rather non-specific inflammatory changes. Hosts with a higher degree of immunity will, under the same circumstances, develop lupus vulgaris (Fig. 13), also a progredient disease, but one in which most bacilli are being destroyed or are kept from multiplying in the presence of a pronounced granulomatous response with epithelioid cell tubercles. There also is a more or less heavy lymphocytic, inflammatory response, and the two factors usually vary in inverse ratio. By comparing numerous cases of lupus vulgaris, one can construct a graded series from dense lymphocytic infiltrate with few small foci of epithelioid cells to massive epithelioid tubercles with narrow or almost absent lymphocytic mantles.

Logically, the next step is the "naked" epithelioid cell tubercle of sarcoidosis (Fig. 14), and it was first on this morphologic basis that Jadassohn's teachings[7] were developed that sarcoid is a form of tuberculosis with "positive anergy." I do not want to labor this point here, inasmuch as the etiologic relationship between tuberculosis and sarcoid is of no great concern for this purely histopathologic discussion. The pros and cons of this question have been ably set forth by Rostenberg.[12] All I want to point out is the fact that lymphocytic and epithelioid reaction in allergic response to tuberculous infection often vary inversely.

In distinction from the progredient tuberculodermas, the so-called tuberculids are self-limited. It is assumed that they result from embolism of small numbers of bacilli which are either dead on arrival or soon succumb in a skin that has a high degree of immunity. The effect is similar to that of a tuberculin injection. Among the various clinical forms, we can again construct a graded series.

The smallest and most innocuous member is *lichen scrofulosorum* (Fig. 15). Presumably caused by the lodging of a few bacilli in small superficial or perifollicular capillaries, it is characterized under the microscope by minute tubercles. Sometimes these are well developed, sometimes there are only a few epithelioid cells in addition to non-specific inflammation. The picture actually is similar to that of a tuberculin reaction of moderate intensity. Papulonecrotic tuberculid (Fig. 16), on the other hand, resembles the sloughing reaction to an overdose of tuberculin in a highly allergic individual. There is primary tissue necrosis — not secondary

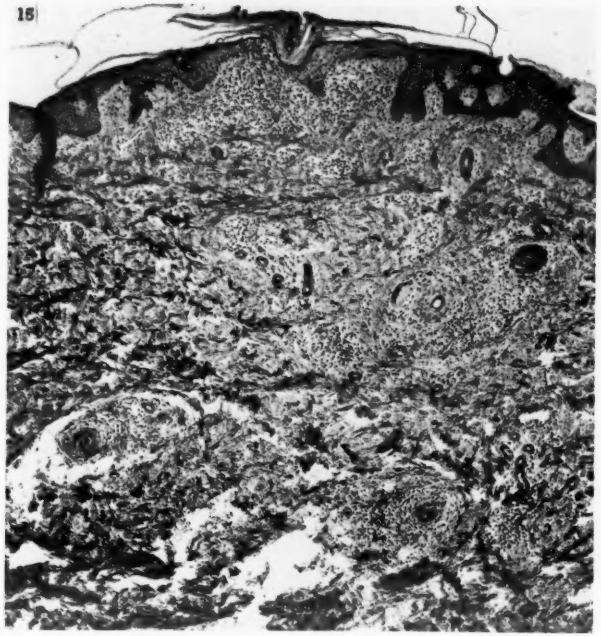

Fig. 15. Lichen scrofulosorum. Center of papule topped with parakeratotic scale. Fairly mild tuberculoid infiltrate around blood vessels and hair follicles.

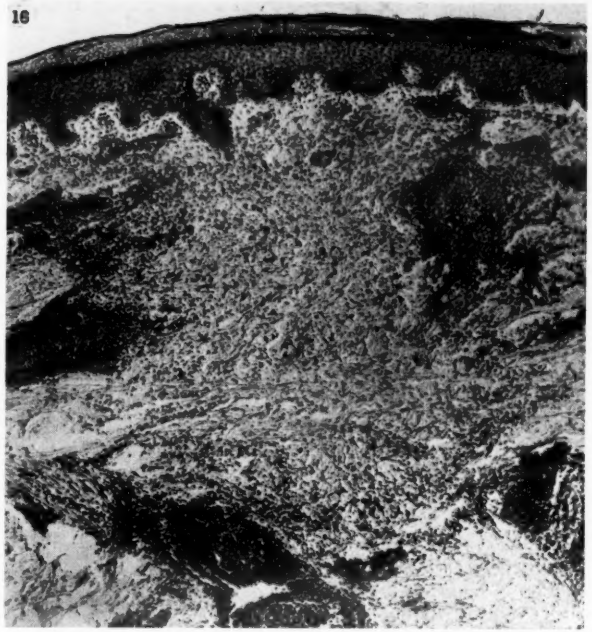

Fig. 16. Papulonecrotic tuberculid. Large area of primary necrobiosis in the upper corium. This area is surrounded by histiocytes and lymphocytic infiltrate. In other cases, complete tissue necrosis and elimination of the slough to the outside may be found.

caseation — in the corium, and around this a more or less pronounced wall of tuberculoid granulation tissue develops. In the clinically most severe type, erythema induratum, a deep tuberculous phlebitis is complicated by secondary changes, often necrosis, in the fat tissue, and these changes are associated with a massive foreign body reaction.

It is of interest to note that essentially similar reactions are elicited by dead as well as live, avirulent as well as virulent acid fast bacilli, if these are deposited in the skin of allergic individuals. That the allergy can be produced only by living bacilli is outside the scope of our discussion. More or less similar tissue responses are found in infections with other micro-organisms, such as Hansen's bacillus, the treponemas of syphilis and yaws, various fungi and others.

Perhaps even more interesting is the result of the recent work of Gell and Hinde[6] who analyzed the tissue reaction in the Arthus phenomenon. They demonstrated two phases. One is a histiocytic reaction which in some stages is similar to the epithelioid response of tuberculin type sensitivity, and which occurs in skins of moderate sensitivity. The other one is an acute necrotizing inflammation, preceding the first-named in the fully sensitized animal. Last year Korngold and his co-workers[9] showed by means of radioactive allergen, that injected foreign protein actually is fixed in skins that have been sensitized. The combined findings of these workers seem to indicate that even soluble proteins can elicit a tuberculin type response if they are deposited in the substance of the skin and are retained there for a considerable period of time. A bridge is thus established between the granulomatous reactions caused by corpuscular antigens such as microorganisms and the somewhat similar granulomatous pictures which we discussed earlier in allergic granulomatosis and in which one might presume a fixation of soluble antigens in the skin.

A few remarks finally may be devoted to two special cases, namely insect bites and the eczematous dermatophytids. In reaction to arthropod bites (Allington and Allington[2]) tissue response is primarily caused by the specific toxic action of the injected secretion. However, a strong factor of individual acquired resistance or hypersensitivity enters the picture. The reaction may vary from complete anergy, over fleeting urticarial lesions and more persistent papular infiltrates, to bullae on the one hand and persistent granulomas on the other. Histologically, there often is some central necrosis, even in relatively mild inflammatory lesions. The granulomatous infiltrates usually are characterized by large numbers of reticulo-endothelial cells and eosinophils, so much so that they may be confused with lymphoblastomas (Winer and Strakosch[18], Allen[1]). These lesions may be another instance of granulomatous reaction to a locally fixed antigen, possibly even to retained parts of the parasite, as in tick bites.

Eczematous dermatophytids, on the other hand, seem to show that specific sensitization of one tissue, in this case the epidermis, manifests

itself in similar fashion regardless of the route by which the antigen is carried to the skin. The so-called dyshidrotic vesicles of the palms and soles in this type of eruption have all the characteristics of eczematous contact-type dermatitis modified only by the special terrain of exceptionally thick epidermis and keratin layer. They have no relation to the sweat ducts (Devine,[5] Wilson and Thackray[17]).

SUMMARY

I have tried to give you a cursory review of tissue responses as they are found in allergic dermatoses. I know I am guilty of omissions and simplifications, and — probably worst of all — of drawing parallels and finding connections without sufficient proof. I felt justified in doing so because I wanted to show you the associations and deliberations that take place in one dermatopathologist's mind while he analyzes an unknown slide and meanwhile speculates concerning the reasons for morphologic similarities and dissimilarities.

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12 E. 4th Street

TOPICAL USE OF HYDROCORTISONE ALCOHOL IN THE TREATMENT OF RAGWEED HAY FEVER

Preliminary Report

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THE ABILITY of orally administered cortisone and parenterally administered ACTH to exert an ameliorating action in allergic nasal tissue[2,3] led to the hope that cortisone might be equally valuable when topically applied (ACTH is only effective parenterally). Dill and Bolstead[4] reported a significant improvement in slightly less than half of a series of patients treated topically with cortisone, and Seidmon and Schaffer[8] recently reported that topically applied cortisone in combination with an antihistamine resulted in good to excellent subjective relief in 86 per cent of patients treated; the antihistamine alone gave equal relief in 78 per cent. Myers[7] observed that the injection of cortisone or hydrocortisone into nasal polyps resulted in the disappearance or marked reduction of polyps, and did not cause undesirable side effects. Semenov,[9] however, after applying cortisone by sprays, drops, and packs, not only concluded that this treatment was valueless, but also reported severe side reactions, characterized by substernal pressure, flushing, and collapse, following the injection of cortisone into nasal polyps. Williams[13] also emphasizes the dangerous side effects which may follow the use of hormones in treating diseases of the ear, nose and throat. Another therapeutic disadvantage of cortisone results from the fact that its insolubility necessitates preparing a suspension rather than a solution of the steroid, and it is extremely difficult to distribute a particulate suspension evenly over the nasal mucosa.

Hydrocortisone is closely related chemically to cortisone, differing only in that it has a hydroxyl radical, rather than a ketone group, in the eleventh carbon position of its nucleus. This very slight chemical difference is, however, of considerable physiologic importance. Hydrocortisone is about twice as potent as cortisone[5]; but since there seems to be a disassociation between its anti-inflammatory and other physiologic effects, this greater potency is not accompanied by a higher incidence of side reactions.[1] Consequently, small doses of hydrocortisone are as effective as larger doses of cortisone, but are much less likely to produce symptoms of hormonal excess. In addition, the steroid has proved of marked value when applied locally to inflamed tissue.[6,7,10,11]

Hydrocortisone alcohol is soluble in water and, therefore, lends itself to nebulization or to nose drop administration. A preparation containing an extremely dilute (.020 per cent) solution of hydrocortisone alcohol in combination with two vasoconstrictors (hydroxyamphetamine hydrobromide .5 per cent and phenylephrine hydrochloride .125 per cent)*

*Vasocort, Smith, Kline & French Laboratories.

recently became available for investigational use. Since the effect of topically applied hydrocortisone on inflamed nasal tissue has not been ascertained heretofore, it was decided to conduct a study to determine what benefit, if any, this preparation would have on the allergic nasal membrane.

METHOD

This study was conducted from August 27 to September 14, 1953, on twenty-five patients who suffered from severe or moderately severe symptoms of ragweed hay fever, and who had failed to respond adequately to previous desensitization or antihistamine therapy. The patients ranged in age from three to fifty-five. Seven were children under twelve; the majority were young adults. Medication was administered by drops and by means of a plastic spray bottle; the initial dose was one dropperful (the dropper is dosage adjusted) or three squeezes of the spray bottle in each nostril every three hours (both methods deliver about 0.2 cc to each nostril); later, the medication was taken as needed. Each patient was examined at least twice a week during the course of the study.

Objective response to medication was determined by direct observation of the nasal membrane. If there was evidence of marked beneficial changes in the pallor or bogginess of the membrane, the patient was considered improved. If there was no—or equivocal—evidence of a beneficial change the patient was considered unimproved.

Subjective response was determined by interviews during which the patients reported on the efficacy of the medication in causing relief of blockage, the lessening of rhinorrhea, and the decrease of sneezing.

RESULTS

In evaluating the objective response to the medication, no attempt was made to grade this response as "good," or "excellent" because—although some patients did evidence a singularly beneficial response—it was felt that this method of evaluating objective results is of dubious statistical value when applied to a comparatively small series of patients. Then, too, there are no generally accepted objective criteria for determining when "good" stops and "excellent" begins and, in the end, the degree of response depends to a great extent on the subjective bias of the observer. Therefore, objective results are listed as either "improved" or "unimproved."

The subjective results of this study are graded according to the patient's report of the degree of relief obtained. The objective criterion on which these evaluations were finally based was the duration of effective relief of nasal blockage. If, in addition to causing a significant lessening of sneezing and rhinorrhea, the medication caused a relief of nasal congestion lasting for from seven to ten hours, the response was considered "excel-

lent"; from five to seven hours, "good"; from three to five hours, "fair"; less than three hours, or relief of nasal blockage not accompanied by relief of other symptoms, "poor." Two patients who had only a fair relief of nasal blockage, but who had a dramatic relief of other symptoms, were also considered to have obtained a good result.

TABLE I. RESULTS OF TREATMENT

Patient	Subjective Response	Objective Response	Side Effects
R.B.	Excellent	Improved	None
M. D.	"	"	"
F. R.	"	"	"
C. L.	"	"	"
S. D.	"	"	"
L. B.	Good	"	"
M. V.	"	"	"
J. B.	"	"	"
C. C.	"	"	"
N. R.	"	"	"
B. A.	"	"	"
N. D.	"	"	"
O. C.	"	"	Slight sneezing
D. S.	Fair	"	None
B. C.	"	"	"
K. C.	"	"	Irritation early in course
M. B.	"	"	None
S. P.	"	"	"
M. B.	"	"	"
S. G.	Poor	"	"
V. Z.	"	Unimproved	Irritation with resultant sneezing
R. N.	"	"	None
R. H.	"	"	"
N. M.	"	"	"
B. D.	"	"	Irritation with sneezing

Of the twenty-five patients, twenty experienced a beneficial, objectively evidenced response to the medication. Of these twenty, all but one claimed a significant subjective response. Five patients showed no objective improvement. Four patients (two of whom experienced objective improvement) complained of a transient irritation and sneezing following the administration of the medication (Table I). There was no evidence of tissue rebound.

Nineteen of the twenty-five patients experienced a subjective relief which was considered "excellent" in five; "good" in eight; "fair" in six. Subjective results were poor in six patients, one of whom showed a beneficial objective response to the medication (Table I).

DISCUSSION

The results of this brief, preliminary study indicate that, for a majority of patients, the medication is a highly effective treatment for ragweed hay fever. Assessment of the particular role played by the hydrocortisone alcohol component of the medication must, of necessity, be somewhat inconclusive because of the uncontrolled nature of the experiment. The small number of patients treated, and the short length of time the study was conducted, made the use of controls infeasible. However, previous use of each of these vasoconstrictors alone (both are standard drugs which have long been available) indicated that they were of very limited value in treating pollen allergy, and often caused a tissue rebound which ultimately increased rather than lessened congestion. Therefore, one of the most surprising results of the study was the ability of the vasoconstrictors in combination to provide rapid and unusually long lasting relief of nasal blockage free from tissue rebound. In the light of work done on the adrenocorticotropic hormones by other investigators, it does not seem unreasonable to attribute the ameliorating tissue changes which usually accompanied this subjective relief to the action of hydrocortisone alcohol.

Because beneficial tissue changes may occur for reasons other than the effect of medication, there is always some possibility of error in interpreting objective results; however, it is felt that the conditions under which this study was conducted did much to lessen this possibility. All patients had failed to show an adequate response to desensitization and/or antihistamine therapy; the study was done at the height of the hay fever season at a period when the ragweed pollen count was constantly high; and only those changes which took place within a week were considered significant.

It was felt that if the study were continued beyond the height of the season it would prejudice the results in favor of the medication (it would be difficult to credit an improvement occurring after the season's end to any one factor) and, therefore, it seemed logical to assume that if the medication did not act quickly, it would be hard to prove that it acted at all.

There were no systemic side effects evidenced in these patients. The side effects that did occur (sneezing, nasal irritation) were infrequent, transient and mild.

SUMMARY AND CONCLUSIONS

Twenty-five patients who suffered from moderately severe to severe symptoms of ragweed hay fever, and who had failed to respond adequately to desensitization and/or antihistamine therapy, were treated with local applications of a medication combining a dilute (.020 per cent) solution of hydrocortisone alcohol and two vasoconstrictors. Significant objective improvement—determined by direct observations of the nasal mucosa—was evident in twenty of the twenty-five patients (80 per cent);

marked subjective relief—including, in five patients, relief of nasal blockage for as long as seven to ten hours—was reported by nineteen patients (79 per cent). Four patients suffered from a mild, transient irritation and an increase in sneezing. No other side effects were noticed; there was no evidence of tissue rebound.

It is felt that the following conclusions can be drawn from this study:

1. Hydrocortisone alcohol, even in a dilute solution, exerts a definite ameliorating action on the allergic nasal mucosa.

2. The medication provides rapid and prolonged nasal decongestion without causing tissue rebound.

3. The medication is a highly effective treatment for ragweed hay fever; it has proved valuable in relieving symptoms which had not responded adequately to antihistamine or desensitization therapy.

4. The medication provides marked symptomatic relief; it does not cure the condition.

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BRONCHIAL ASTHMA COMPLICATED BY ACUTE UPPER RESPIRATORY TRACT INFECTION TREATED WITH THE HYDRIODIDE OF DIETHYLAMINOETHYL ESTER OF PENICILLIN G (NEO-PENIL®)

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THERE has been considerable speculation and investigation[20,21] as regards the trigger-like mechanism effect which the acute upper respiratory infections have on allergic bronchial asthma. Many therapies[2,10,14] have been employed prophylactically in a diligent effort to protect these allergic patients in order that they might avoid severe paroxysms of asthma. These preventive efforts are applied prior to or during the infection. It is well known that in spite of the specific attempts of protection by immunization with cold, influenzal, and autogenous vaccines, antihistamines combined with aspirin, and human gamma globulin, attacks do occur. Associated frequently with these episodes of status asthmaticus, are infections in the nasopharynx, nasal accessory sinuses, tonsils, adenoids, and the broncho-pulmonary tree.

Lately, the best efforts in prophylaxis in upper respiratory infections have been accomplished by the use of antibiotics.[3,15,18] Since Neo-Penil® had proved to produce high levels of penicillin in the sputum and bronchial secretions,[4,6,13] it was felt that the drug would be ideal in aborting upper respiratory tract infections, and thus decrease the incidence of acute asthma and status asthmaticus. Experiences with Neo-Penil in chronic bronchial asthma and emphysema have been reported.[4,6,11,16,17]

MATERIAL

Eighty-two patients varying in age from twenty to seventy-two years were followed in the Allergy Clinic from January, 1952, until December, 1953. They were selected from a group of four hundred veterans previously studied.[8] Those patients were selected from the clinic who were proved to have chronic bronchial asthma. They had given a history of, or had been treated for, one or more acute episodes of asthma following an acute upper respiratory tract infection in the past. Fifty-two of the group gave a history of having had severe enough symptoms to require hospitalization, in spite of their routine treatments with bronchodilator drugs.

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Presented by title before the Decennial Congress of the American College of Allergists, Miami Beach, Florida, April 8-10, 1954.

Most of these severe attacks occurred while the men were in the service and prior to coming under our care.[8]

METHOD

The patients were instructed to report the first evidences of acute upper respiratory tract infections as soon as they occurred. Group I patients were given 500,000 units of Neo-Penil®, and later 300,000 units intramuscularly, daily for three days. Group II patients were given regular Potassium Penicillin G in equal amounts for three days. Group III patients were given no antibiotics unless their fever became elevated and then were given Oxytetracycline orally.

All patients were given a complete physical examination, including cytologic study of the nose and sputum secretions, roentgenograms of the nasal accessory sinuses, and of the chest. All patients were receiving perennial desensitization with inhalants, pollens, and molds. Fifteen were receiving respiratory and physical exercises,[1,9] as part of the prophylactic routine for asthma. Numerous nasal smears were made to establish the presence of infection, and frequent consultations were held with the Otolaryngologist, in an attempt to recognize and localize early infection. The persons in Groups I and II having smears which demonstrated large numbers of neutrophils, were given immediate treatment, as this was considered to be an infectious rhinitis.

TABLE I. CLASSIFICATION OF ACUTE ASTHMA RESULTING IN EACH GROUP

Group	Number of Cases in Ea. Group	Type of Penicillin Received	Severity of Asthma		
			Mild	Moderate	Severe
I	30	Neo-Penil®	5(20%)	3(10%)	3(10%)
II	19	Potassium Penicillin G.	5(30%)	3(15%)	2(10%)
III	33	None	10(30%)	8(24%)	3(9%)

RESULTS

Table I shows the number of cases followed and the type of penicillin used in each group. The resulting asthma in each group following infection is classified according to severity. It is seen that those cases receiving Neo-Penil®, developed 10 per cent less mild cases of asthma than either the Potassium Penicillin G group, or the control group. Five per cent less moderate cases than the Potassium Penicillin K group, and fourteen per cent less than the control group. Approximately the same number of severe cases developed as in the other two groups.

Table II shows that Group I (Neo-Penil® Group) developed eleven cases of asthma or 37 per cent, and Group II (Potassium Penicillin G Group) developed ten cases or 53 per cent, and Group III (Control Group) de-

veloped a total of twenty-one cases or 63 per cent. There was only a slight difference noted in each group in the number requiring hospitalization, that being 1 per cent less in the Control Group treated with Oxytetracycline. It is seen that this new form of penicillin decreases the total incidence of asthma resulting from upper respiratory tract infections.

TABLE II. CASES DEVELOPING ACUTE ASTHMA AND THOSE NEEDING HOSPITALIZATION

	Group I	Group II	Group III
Total Cases	30	19	33
Acute Asthma	11(37%)	10(53%)	21(63%)
Hospitalized	3(10%)	2(10%)	3(9%)

TABLE III. COMPARISON OF THE INCIDENCE OF ACUTE ASTHMA IN THE PENICILLIN GROUP AND CONTROL GROUP. ACCORDING TO SEVERITY

Classification	Penicillin Groups I and II 49 Cases	Control Group III 33 Cases
Mild	10(20%)	10(30%)
Moderate	6(11%)	8(24%)
Severe	5(12%)	3(9%)
Totals	21(43%)	21(63%)

Table III compares the incidence and types of asthma between the penicillin groups I and II with that of the Control group III. Without penicillin, there were 10 per cent more cases classified as mild, 13 per cent more among the moderate cases, and 3 per cent less among the severe cases. In Groups I and II, twenty-one cases, or 43 per cent, developed asthma, as compared with the Control group of twenty-one cases, or 63 per cent. A 20 per cent higher incidence of acute bronchial asthma was seen to develop in those cases of chronic bronchial asthma, at the onset of respiratory infection, not given penicillin prophylactically.

DISCUSSION

Upper respiratory tract infections in normal persons usually do not cause incapacitation. This is generally not true in persons with chronic bronchial asthma.[19] The infection sets off a series of events which may result in incapacity from seven to ten days or more. To prevent these episodes, the antibiotic Neo-Penil® was used, because of its ability to concentrate in the sputum and bronchial tree. Iodides have been used as an efficacious remedy for asthma for many years, and penicillin for its prolonged antibacterial effect. It was hoped that this new antibiotic-iodide could prevent the progress of the infection to the purulent state, at its on-

set, and aid in the liquefaction of the tenacious bronchial secretions which cause asthma. Other investigators[4,6,11,12] had evaluated this drug in the chronic bronchopulmonary infections and recommended their use. It is seen that this study shows a lesser incidence of acute asthma by the use the antibiotic, as compared with the regular Potassium Penicillin G. Subjectively, this drug was found to loosen the secretions better than ordinary types of penicillin. Both penicillin treated groups showed no pneumonic complications in any of the hospital cases and one case of bronchopneumonia in the control group. This drug has certain definite superiorities over ordinary penicillin in bronchial asthma.

Despite an occasional severe reaction,[5,7] the drug was well tolerated and no reactions were directly attributed to the iodide portion of the drug. During the first six months of this study, a frequent complaint was pain, at the site of the injection, within a short time. This was not noted in subsequent allotments of the drug, and the use of 300,000 units instead of 500,000 units, reduced this to a minimum.

SUMMARY

1. Eighty-two cases of chronic bronchial asthma were studied to determine the effect of Neo-Penil in preventing acute asthma when complicated by acute upper respiratory tract infections.

2. It was found that the hydriodide of diethylaminoethyl ester of penicillin G was more effective in a selected group of these patients as compared to another group given potassium penicillin G.

3. Although there have been reactions reported to the iodides, we did not encounter any in this series.

4. The use of this drug is advocated in reduced dosage (300,000 units) in chronic bronchial asthma, complicated by acute upper respiratory tract infections, to reduce the incidence of acute asthmatic paroxysms.

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RED CROSS DENIES BLOOD SALE CHARGE

Last month, the American Red Cross emphatically denied printed reports that it is charging for blood furnished to hospitals and civilian and military institutions. In the last fiscal year, 88,036 pints of Red Cross blood were furnished without cost to government hospitals, including those for veterans and the Armed Forces. At present, the blood program serves about 3,500 hospitals throughout the United States. According to Dr. David N. W. Grant, Medical Director of the Red Cross:

"Throughout the entire history of its blood program, no charge has ever been made by the Red Cross to hospitals or individuals for blood or blood products. The Red Cross wishes to emphasize that no change has been made in this policy. . . . Every pint of blood donated to the Red Cross has cost the organization an average of $5.12 for its collection, processing, and distribution to hospitals. . . . The present plan of sharing with hospitals concerned a limited portion of this cost, involving supplies which can be used only once and blood transportation charges, is an adjustment to meet local conditions which was worked out with hospital authorities. Approximately ten of the forty-five Red Cross regional blood programs have made this adjustment. . . . In most instances, the hospitals have absorbed these extra costs without passing them on to the patients. . . . The only purpose of the Red Cross in this program is to provide urgently needed blood to the American people. . . . In addition to furnishing about 40 per cent of the whole blood used in this country, the Red Cross Blood Program also provides gamma globulin and other blood derivatives."

OBSERVATIONS ON ALLERGIC SINUSITIS IN CHILDREN

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THE CLINICAL picture of allergy of the nose and paranasal sinuses in children does not differ essentially from that seen in adults. However, the inability of the child accurately to describe his symptoms necessitates greater emphasis upon objective findings. Whereas in the adult a careful history is the most important single procedure in the determination of an allergic etiology, it has been found in dealing with children that the clinical examination and cytologic studies are the more valuable procedures.

In the clinical examination of the nose and sinuses of children one considers the appearance of the mucous membrane of the nose, nasopharynx and pharynx, and the presence or absence of secretion in any of these areas. It has often been observed that in fewer than half of these young patients will one see the pale, edematous mucosa thought to be typical of allergy. Many children are brought for the initial examination during an acute episode which is often due to infection. Others may present a post-nasal discharge or throat complaints rather than nasal symptoms, in which case the mucous membrane of the nose may be quite normal in appearance. The frequency of this occurrence indicates the extent to which one must rely on cytologic studies of the nasal and sinus secretions for correct diagnosis.[4] X-ray studies of the sinuses in children are generally less reliable than they are in adults because of the thickness of the bones of the face.[2,3] In the few instances in which roentgenograms are important in older children, the introduction of a radio-opaque solution by displacement has been helpful in clarifying the changes seen.

Acute infectious diseases sometimes disturb the allergic equilibrium of children, precipitating more severe manifestations of respiratory allergy or developing new sensitivities in another shock organ. Thus a child with a previous mild nasal allergy may develop marked nasal and throat symptoms as a result of involvement of the sinuses, or the lower respiratory tract may become involved with the inception of asthma or bronchitic symptoms for the first time. In my experience measles and whooping cough are the diseases most commonly associated with the worsening of respiratory allergy. Scarlet fever is now so well controlled by penicillin that it rarely causes such an aftermath.

One of the problems most frequently encountered in daily office practice is that of the child who is brought in because of frequent colds. Here it is particularly important to be able to observe the child over a period of time before drawing definite conclusions about a possible allergic factor

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in any given case. Microscopic study of nasal secretion and sputum will be especially helpful in deciding whether the doubtful cases are due to allergy, infection, or a combination of both. When the author has finished looking at the cells under low or high power, he usually switches to the oil immersion lens to determine the presence or absence of bacteria and whether or not organisms are abundant. The amount of mucus present on the slide is also a useful criterion, for allergic membranes whether stimulated by antigens or bacteria usually pour out an abundant amount of mucus. In the rare cases in which there are many organisms and little or no mucus, the sinusitis is usually severe and harder to cure.

Perhaps the simplest part of this cold problem, and also the most gratifying from the standpoint of treatment, is encountered in the child who is sensitive to dust or one of the other inhalants, and whose so-called colds are confined to the fall or winter months. Most of these children respond promptly to dust therapy and the most elementary prophylaxis in the bedroom. Very often only six or eight injections are required during the season, usually in the dilution of 1-1 billion or 1-100 million. If bronchial symptoms are also present then a higher dilution is employed.

In general it may be said that the cold problem of the allergic child is much improved by the adequate control of the allergic factor. You have all observed that the child whose hay fever is well controlled has relatively little trouble with colds in winter. It has also been my experience that allergy of the nose is not frequently complicated by sinusitis unless the nasal allergy has been allowed to go unchecked for a long time. Even when there has been pus in the nose for many weeks it is amazing to see how quickly the child recovers following a few irrigations by displacement, using a simple vasoconstrictor like ephedrine or tuamine.

Although allergic sinusitis in children is most often due to inhalants, food sensitivity is important in many cases, particularly when the nasal symptoms are not related to change of season. In the diagnosis of food allergy in children multiple skin tests are to be avoided if at all possible. Sometimes important clues are derived from the history, but more often it is necessary to employ elimination diets and clinical food tests. The author finds himself giving fewer and fewer skin tests for foods since using the individual food test as outlined by Rinkel.[5] The foods most commonly tested for in children are wheat, milk, chocolate, egg, peanut, corn, orange and potato. In many children tolerance for the offending food is soon developed after a relatively short period of avoidance, and it is important not to break down this acquired tolerance by too frequent use of the food in question.

The tonsil and adenoid problem is so frequently encountered in the management of allergic rhinitis and sinusitis in children that perhaps some mention of it should be made here.[1] Generally speaking, the indications for tonsillectomy and adenoidectomy in the allergic child are no different from those in the child who is not allergic. If there is definite clinical evidence

of chronic infection in the tonsils and adenoids, with obstruction of the nose and eustachian tubes, and a history of recurrent acute episodes, then it seems apparent that surgery is called for, whether or not the child has a co-existing nasal allergy. The only important difference is in the preparation of these children for surgery. The allergic child should have adequate allergic management prior to operation, and if pollen sensitivity is present the surgery should be performed out of the pollen season. When these precautions have been taken the author has never seen any untoward effects as a result of a tonsillectomy and adenoidectomy in an allergic child. Sometimes it happens that a child is sent to the otolaryngologist for a tonsillectomy because of repeated colds, throat irritation and post nasal discharge causing a constant cough or attempt at clearing the throat. Examination of such a child may reveal tonsils and adenoids of normal appearance, and a nasal allergy which has been overlooked and is responsible for all of the symptoms. Allergic management in these cases will usually give prompt relief from symptoms, and operation is not necessary.

It is just as important to continue the allergic management of the child after tonsillectomy as it is to institute it prior to surgery. If this is neglected a regrowth of lymphoid tissue in the nasopharynx or pharynx often results. The author recalls four cases in which a considerable regrowth of adenoids occurred several years after tonsillectomy and adenoidectomy were performed. In each instance the child was found to be free of adenoid tissue during the first year after operation, and subsequent regrowth occurred in one child as the result of uncontrolled hay fever, and in the other three children following repeated colds and uncontrolled dust allergy.

In conclusion it may be stated that the problem of allergic sinusitis in children has developed into one of the more gratifying chapters in the history of our specialty. With adequate allergic management, attention to nutrition, and the prompt control of infection as it arises by antibiotics when indicated, the child with allergic rhinitis or sinusitis may pass through a reasonably normal childhood without developing serious irreversible changes in his upper or lower respiratory tract as he reaches adult life.

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806 May Building

THE COLICKY BABY

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THE SYNDROME of colic in early infancy causes much frustration to the pediatrician and worry to the parents. The effects of colic may continue into later infancy as Spock[11] has noted in his report on "Chronic Resistance to Sleep in Infancy." The baby may become an "Old Man of the Sea," dependent on constant body contact with the conscientious mother who refuses to let the infant cry for long periods. Colic is the most common reason that parents "change doctors" for the newborn infant. The "colic syndrome" is a disease, but is treated often as a special kind of joke. Many hours are used in medical schools to discuss reticuloendotheliosis and other diseases of similar infrequency. The physician often hears his first advice about "colic" in the hospital corridor from a wryly amused older practitioner.

Perhaps the reason that little time is spent teaching the subject is that the academician is shielded from the problem. The professor rarely hears the anguished voice of a mother bewailing her child in the dark hours. Even the residents and the student nurses do not hear the evidence all around them because they think that tense people have all the colicky offspring and *they* don't take care of tense upper-class babies. Yet, if the house officers bore the fixed responsibility to the parents which the practitioner must shoulder, they might discover many colicky patients among the clinic babies. Levin[7] intimated as much in his report on "Colic in Institutions."

What is "newborn colic?" Waldo Nelson[10] writes as a description, "The colic attack begins suddenly; the cry is loud and more or less continuous; so-called paroxysms may persist for several hours; the face is congested and may be somewhat cyanotic, or there may be circumoral pallor; the abdomen is distended and tense; the legs are drawn up on the abdomen, although at times they may be momentarily extended; the feet are often cold; the hands are clenched and the arms flexed and drawn to the body."

Several causes of colic are listed in the pediatrics texts. Aerophagia, improper feeding techniques, underfeeding, overfeeding, tense parents and tense babies, faulty intestinal fermentation of carbohydrates and "neuropathic diathesis" are frequently mentioned. Gastrointestinal allergy has been said to be a rare cause of colic.[1] We have been impressed by the positive family history for allergy elicited in many cases. Frequent oc-

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currence in colicky babies of stool mucus which contained eosinophils and was sometimes bloody, was also noted. The Nance[9] method of staining stool mucus was used. We have made a point of inquiring concerning hay fever, allergic asthma, perennial allergic rhinitis, atopic dermatitis (eczema), frequent and severe sinusitis and migraine headache in the mother, father, siblings, grandmothers and grandfathers, uncles, aunts, and first cousins. We have done this in the case of all the newborn, and the figures presented in Table I concern newborn infants whom we have treated throughout the period of their disease. This table illustrates data we have gathered on these patients.

TABLE I. INCIDENCE OF COLIC

(Infants followed first year of life)

	No. Patients	Colicky Babies	Colic %
Practice	814	308	36.1
Allergic Families	611	367	60.1
Non-Allergic Families	296	74	25.0
Father and Mother Major Allergy	55nb *	43	78.2

*Newborn.

First, we attempted to discover the incidence of colic in our practice. We could not find such figures noted in the literature. Our practice includes a rather broad cross section of social classes and nationalities. Rochester, New York, is a metropolitan area. Skilled technicians, many university elements, laborers, and leisure classes are all represented. Large Anglo-Saxon, Italian, Jewish, Polish, Irish and German groups are present. The over-all incidence of 36.1 per cent was a surprise to us, for we did not think the percentage would be that high.

Second, the 60.1 per cent of colic found in allergic families was much higher than the over-all incidence. Also, the 78.2 per cent of colic found in families where both mother and father displayed major allergies confirmed our impression that allergy plays a large role in this disease.

Third, it can be seen that an important number of families without allergic histories produce colicky infants. This finding coincides with our failure to abolish colic in our practice by placing colicky infants on hypoallergic diets. We experience such failure, of course, even with infants from allergic families.

Certain non-allergic colicky types seem clear cut to us whether or not they have a family history of allergy. (1) The "hypertonic" infant is usually the child of tense, quiet parents. When one pulls the hands of the supine, hypertonic baby, his head comes up on a stiff neck instead of lolling back on a relaxed neck. This is the favorite colic type of the psychiatrist, but is a minority group in our practice. (2) Some infants exhibit marked bilateral ankle clonus and excessive "startle" reflex. Such babies may

have a mild form of tetany. Calcium therapy relaxes these infants. (3) Dr. William L. Bradford,[2] working with Dr. George Heckel, has used progesterone therapy for colic. We have obtained immediate cessation of colic in some babies following this suggestion. He is still working on this aspect of the problem. We know no way of identifying in advance the infant who will respond to such therapy. (4) Occasionally, a stenotic anal membrane offers organic obstruction to the peristaltic rush.[6] Since the gastro-colic reflex is stimulated many times daily in infants, a lengthy period of colic may be present. (5) Some babies seem to exhibit imperative demand for prolonged sucking satisfaction.[8] These five types of colic have a basic interest because, along with allergy, they are a direct result of physiological and emotional immaturity inherent in the newborn human being. Newborn colic has not been called "three-month" colic without reason. It is no coincidence that the above-noted immature reactions are almost always resolved at about three months of age.

Immunological efficiency often changes at about that time.[4] The "hypertonic" infant begins to enjoy the diversion of his hands and the faces of his parents. The calcium-phosphorus relationship becomes more like the adult type as the renal tubular cells handle the excretion of phosphorus more readily.[12] Hormones assume different qualitative and quantitative values.[19] The passage of stool dilates the stenotic anal membrane.

Of course, there are other facets to the colic problem which are important. It is highly essential to make a differential diagnosis. Many non-colicky situations cause infants to cry with pain. Scurvy, otitis media, malrotation of the intestine, intussusception, strangulated inguinal hernia, ureteral colic associated with genito-urinary malformation, infections and sub-dural hematoma are dangerous diseases which must not be overlooked. Also, these conditions may all afflict infants who have colic.

Our treatment of colic is not satisfactory to us. The prophylaxis and treatment of colic as mentioned in textbooks is far from satisfactory.

We have outlined our methods briefly for those who may be interested. We try to hold to our program, but we confess that parents sometimes leave our practice in great dudgeon, their infant still colicky.

This is our therapeutic program:

1. We place the newborn on a soybean formula and synthetic vitamins immediately, if the parents both have major allergies.[5]

2. We do the same if we find that there is an allergic family history and the infant seems colicky.[5]

3. We immediately provide the parents with a sedative for the child such as Demerol or one of the barbiturates, sometimes mixed with Syntropan®, a smooth muscle antispasmodic. A great deal of unreasonable censure has been given to the use of sedation. Sedation of infants is censured most by those who do not keep the nightly vigil with colic-haunted parents.

4. Colic must be explained to the parents at the beginning and reassurance given to them.

5. We treat the infant with ankle clonus and excessive startle reflex as though he had full-blown tetany without convulsions.

6. If the colic is severe, we immediately prescribe 5 milligrams of progesterone twice daily and continue as long as necessary, if effective.

7. We teach the parents to dilate the stenotic anal membrane by the finger, if mild, or we use gum dilators, cautiously, if severe.

8. We advise a pacifier to be used for fifteen to twenty minutes after each feeding, if we feel the sucking reflex is not satisfied.

9. We discontinue the sedative first, when the colic seems under control. We discontinue the progesterone next, to estimate its value in the treatment. We discontinue calcium therapy as indicated by cessation of clonus and excess startle reflex. If the colic is due even in part to allergy, a cow's milk formula is attempted cautiously after four months. Mixed types of colic are frequently present and all factors must be considered and treated.

One must be careful not to create a hungry baby by forgetting caloric intake while calculating other factors. It does seem that the cross-cut nipple sometimes helps to prevent the discomfort of aerophagia. Starting a cereal in the formula early seems to satisfy some infants, particularly large, hungry babies. Closer attention to proper "burping" of the baby may be fairly important sometimes. A small, warm enema given to the baby with the infant rubber rectal syringe can sometimes provide sleep for the parents. We have not been impressed by the role of carbohydrate changes in the treatment of colic.

To conclude, the therapy of infantile colic should be based on alleviating the consequences of immaturity, whether emotional or physiological, but more frequently the latter. As new facts are learned about the newborn period, their application to this problem will be fruitful.

CONCLUSIONS

1. Colic is a very important syndrome of newborn life.

2. Departments of pediatrics in the medical schools do not devote enough time to the infantile colic problem.

3. There are multiple factors involved in the pathogenesis of colic.

4. Allergy is a very important cause of infantile colic as demonstrated by incidence figures.

5. Treatment of colic should be intelligent, based on physiological phenomena known to be present in the newborn period.

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219 Dorchester Road

CIBA ANNOUNCES AWARDS FOR 1954-55

In view of the ever-increasing importance of the medical, biological, and sociological problems of aging, the Ciba Foundation has decided to devote particular attention to this field and is providing awards for papers on "Experimental Research Relevant to the Problems of Aging." Five awards, of an average value of $300 each, are available for the period 1954-55. The announcement of awards will be made in July, 1955. Entries must be received not later than February 28, 1955.

Entries will be judged by an independent international panel of distinguished scientists who will advise the Executive Council of the Foundation on their findings, and will also have the power to recommend variation in the size and number of awards according to the standard of entries. Preference will be given to younger workers.

The work submitted should be unpublished at the closing date for entries. The papers may be in the candidate's own language, but an English summary not exceeding 500 words must be attached. Where there is one or more co-author, the name of the leading author should be indicated.

Details may be obtained upon application to G. E. W. Wolstenholme, Director, Ciba Foundation, 41 Portland Place, London, W.1, England.

THE SOUTHWEST ALLERGY FORUM

The Southwest Allergy Forum will hold its annual meeting January 9-11 at the Marion Hotel, Little Rock, Arkansas. The meeting will consist of panel discussions and round-table discussions of practical interest to allergists, and questions and discussions from the floor will be invited so that a completely informal exchange of ideas can take place. Two social hours and a banquet will round out the program. About one hundred allergists are expected to attend.

A STUDY OF THE DUST, MOLD AND BACTERIA CONTENT OF THE EXHAUST OF VARIOUS TYPES OF VACUUM CLEANERS

A Preliminary Report

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REMOVAL of dust from the home with minimum exposure of the patient to this allergen is an important factor in the control of house dust allergy. Endorsement or condemnation of any commercial product is distasteful to many physicians; however, complete aloofness is not compatible with the physician's responsibility to help his patient in every way possible. For a patient sensitive to house dust, the ideal vacuum cleaner should fulfill three requirements: (1) It should remove the dust thoroughly. (2) There should be a minimum of recirculation of dust from the exhaust. (3) There should be a minimum amount of dust raised in the cleaning process. This study is concerned with the second and third of these requirements.

Much valuable information regarding the first requirement may be found in the periodic reports of national consumer organizations. These reports must be completely factual and impartial. However, they should be studied carefully and followed regularly. For example, in 1947 one organization found the Airway cleaner first in cleaning ability of twenty-one tested, while in the same year another organization found it twenty-sixth of thirty-five tested. Possibly this was due to the fact that one organization used "synthetic" dirt consisting of talc and fine sand, while the other used dirt as it normally accumulated in the home. We must remember also that a brand name is no assurance of a continued high rating. As an instance, the Lewyt cleaner, in 1947, was listed fourth in cleaning ability among twenty-one tested by one organization and was rated "A. Recommended." This continued until November, 1952, when its rating dropped to "B. Intermediate." Then in November, 1953, a new and "improved" model was rated "C. Not Recommended," largely because of excessive wear on carpets by a newly designed rug tool.

PROCEDURE

Thirteen different vacuum cleaners were tested. They were selected only because of their availability to the author, and because they represented as many different types as possible. They may be classified into types as follows: (1) upright, revolving brush or bag type with cloth bag; (2) the same, with paper bag inside a cloth bag; (3) tank type; (4) pot

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or canister type (a modified tank type); and, (5) centrifugation type (the dust is centrifuged into whirling water).

In each test, the cleaner was operated for twenty minutes over five rugs totaling 576 square feet. The interval was five days in each case. Weather

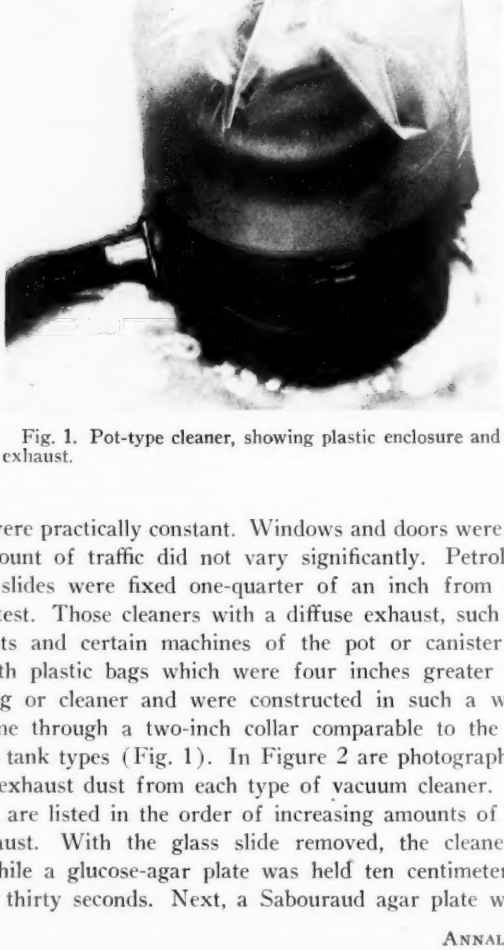

Fig. 1. Pot-type cleaner, showing plastic enclosure and exhaust.

conditions were practically constant. Windows and doors were kept closed, and the amount of traffic did not vary significantly. Petrolatum-coated microscope slides were fixed one-quarter of an inch from the exhaust during the test. Those cleaners with a diffuse exhaust, such as the bag-type uprights and certain machines of the pot or canister type, were enclosed with plastic bags which were four inches greater in diameter than the bag or cleaner and were constructed in such a way that the exhaust came through a two-inch collar comparable to the exhaust on most of the tank types (Fig. 1). In Figure 2 are photographs of typical samples of exhaust dust from each type of vacuum cleaner. In Table I, the cleaners are listed in the order of increasing amounts of dust caught at the exhaust. With the glass slide removed, the cleaner was then operated, while a glucose-agar plate was held ten centimeters from the exhaust for thirty seconds. Next, a Sabouraud agar plate was similarly

TABLE I. SUMMARY OF DATA ON VACUUM CLEANERS

Cleaner	Type*	Dust at Exhaust (least to most)	Exhaust Colonies 30 sec. (sum)	Grams of Dirt in 20 Minutes	Colonies by Sedimentation in 3 Hours (sum)
1. Lewyt	P	1	4	33	—
2. Westinghouse	T	2	4	31	46
3. Electrolux	T	3	13	36	43
4. M. Ward	T	4	43	29	48
5. Filtex	T	5	10	31	34
6. Airway	T	6	35	34	—
7. Hoover with paper bag	U(p)	7	16	102	80
8. Kenmore—third run with new bag	U	8	114	—	56
9. Electrikbroom	U-T	9	—	20	64
10. Hoover with cloth bag	U	10	37	68	37
11. Filter Queen	P	11	25	26	36
12. Kenmore with old bag	U	12	43	23	—
13. Kenmore—first run with new bag	U	13	163	56	—
14. Kirby	U	14	65	53	65
15. Rexair	W-C	15	34	14	60

*In this column, P—pot type; T—tank; U—upright; U(p)—upright with paper bag; W-C—water centrifugation; U-T—upright-tank (bag but no revolving brush).
See Figure 1.

There were no significant variations among the cleaners in the amount of dust by sedimentation in ten hours or in the amount of dust caught near the tip of the "wand."

exposed. The sum of the colonies which developed is given in Column 3 of Table I.

For comparative information as to the amount of dust stirred up in the cleaning process, petrolatum-coated slides were exposed in two rooms for ten hours during and after each cleaning (Column 6, Table I). Glucose-agar and Sabouraud agar plates were also exposed for three hours during and after cleaning (Column 5, Table I). Petrolatum-coated slides were attached to the "wand," two inches from the floor, during the cleaning process. This was done especially to compare the amount of dust stirred up by the beater action of the revolving brush of the upright cleaners with that obtained by the straight suction of the tank types. No definite difference in the two types was noted. The weight of the dust collected in each twenty-minute test is shown in Column 4. It was not the purpose of this study to rate cleaning ability, and no especial accuracy is claimed for these figures. They are shown only because they are of interest in relation to the amount of dust from the exhaust. The weight of dirt removed by each cleaner would vary somewhat, according to the amount removed by the previous cleaner in this series.

Three test checks were made on each of the following: Electrolux, Kenmore, and Rexair; two were made on the Airway, Filtex, Ward, Hoover (with paper bag), Kirby, Filter Queen, and Lewyt; and one each on Westinghouse, Electrikbroom, and Hoover (with cloth bag).

DISCUSSION

We should consider the problem of dust removal first from the standpoint of those cases in which the dust-sensitive patient is the one who must operate the cleaner. In such cases, the amount of dust which is recirculated from the exhaust is of some importance. It should be noted, however, that the actual amount of exhaust dust is exceedingly small

Fig. 2. Examples of exhaust dust from each type of vacuum cleaner: (a) pot type; (b) tank type; (c) upright with paper bag; (d) upright; and (e) water centrifugation.

compared to the amount removed from the home, even in those cleaners with the least efficient filter. Several attempts to weigh the exhaust dust were unsuccessful. It may well be that the amount of dust stirred up in the cleaning process, particularly by those cleaners in which the exhaust is discharged as a blast of air along the floor, is more important than the amount of recirculated dust. In this respect, the pot-type and upright-type cleaners have a definite advantage over others. However, although the amount of dust escaping from the upright or bag type of cleaner was surprisingly small, a distinct and objectionable odor of dust was noticeable from all cleaners with a bag which had been in use a long time. The housewife who must do the cleaning can minimize most of these objections by wearing an efficient filter mask.

For the dust-sensitive patient who is not required to do the cleaning, the above considerations are of little importance. No significant differences were found among any of the cleaners in the amount of dust which settled in ten hours, during and after the cleaning. No figures are reported, because they would give a false impression of accuracy. The most important factor for the patient who can leave the house during the cleaning is the total amount of dust removed. We must remember that a cleaner which removes dust slowly may eventually remove a satisfactory quantity, if it is operated for a sufficient time. It would seem from this study that a patient would be wise to select a cleaner primarily on the basis of cleaning ability, quality, and convenience, and only secondarily on the basis of any supposed therapeutic benefit. From the studies reported here on an old Kenmore cleaner (subsequently overhauled), as well as from other studies not reported herein, it can be stated that such an adjustment and overhaul may make the purchase of a new cleaner unnecessary.

SUMMARY

Thirteen different vacuum cleaners representing five general types were tested. The amount of dust, mold and bacteria which escaped from the exhausts varied markedly, but was nevertheless very slight, even in those which discharged the most dust, compared to the total amount of dirt removed. The amount of dust stirred up by those cleaners in which the exhaust escapes as a blast of air along the floor may be greater than the amount which escapes in the exhaust air itself. No significant differences were found among any of the models in the amount of dust which settled out from the air in the room during and after the tests. It would seem, therefore, that the amount of dust in the exhaust and also the location and force of the escaping air might be of some importance to the dust-sensitive housewife who fails to wear a filter mask. For those members of the household who can be absent during and for a short while after the cleaning, the only important factor is the thoroughness of the dust removal.

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OTOLOGIC MANIFESTATION OF ALLERGY

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MANY ORIGINAL investigators during the past few decades have steadily implicated allergic factors as possible etiologic bases of all types of otologic pathology. Today the practice of otology requires a knowledge of measures for the prevention, diagnosis and treatment of allergic manifestations. Whether the otologist works with the allergist, or applies adequate methods himself, is less important than that ear pathology not be permitted to continue unimproved, or to continue to recur, by failure to consider allergy as having any relation to it.

Some otolaryngologists consider allergy to predominate in 70 to 80 per cent of nasal and sinus conditions. Since many otologic problems arise directly as complications of nasal and pharyngeal conditions, it therefore becomes a direct cause, whether by direct extension of the antigen-antibody reaction in the mucous membrane, or by development of infection in the middle ear.

Jordan[5] has reported that of 727 otological conditions seen during one year, 27 per cent were caused or complicated by allergy. Although this percentage varies widely for different types of conditions and parts of the ear involved, any otologic pathology may be either of allergic origin or complicated by allergic manifestations.

EXTERNAL EAR

Otitis externa, involving the skin-lined canal, is usually of infectious origin, but at times persistence of the infection may be related to bacterial or fungal sensitivity. Purulent drainage from pale, boggy, macerated skin or a localized furuncle indicate infection. Dry desquamating skin with a corrugated appearance, the removal of which leaves a hyperemic or excoriated surface, usually indicates fungus infection, with or without visible colonies of fungus growth. Allergic components should be considered in any condition which fails to resolve completely under adequate antibacterial or antifungal therapy. Difficulty in totally eliminating fungus infection may be due to a localized skin sensitivity in which usual resistance is absent, and contact with spores in the intimate environment results in reinfection. Treatment by injection of fungus extract often aids in permanent elimination.

Atopic dermatitis is manifest by roughened, itching areas of variable extent which involve the external auditory canal in the same manner as any other localized area of skin surface. It may result from either food

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or inhalant antigens. Derlacki[3] found one case to recur every time pork was eaten.

Contact dermatitis may also occur in the outer ear canal, but more frequently involves the concha, auricle or periauricular region. Patch tests, as indicated by the history, may be positive only on, or immediately adjacent to, the auricle.

Prolonged treatment by surface application of chemicals and antibiotics may result in acquired drug sensitivity. Less frequently this condition may follow oral medication.

MIDDLE EAR

Acute otitis media in infants and children, which may recur every few weeks in winter, is almost always secondary to pharyngeal conditions. Chronic pharyngeal allergy, manifest by hyperplasia or allergic edema of the lymphoid tissue throughout Waldeyer's ring, is most frequently due to a food, and is even more common as a cause of middle ear infection than is chronic infection in the tonsils and adenoids. Although immediate treatment of the otologic infection is necessary, permanent relief demands a determination of the basic pharyngeal pathology and its elimination.

CASE REPORTS*

Case 1.—S. G., a four-month-old boy, was seen in February, 1952, with a history of drainage from the left ear a month previously and a recurrence the night before. Nasal drainage had been present a week. The parents had decided that "injection of penicillin relieved the head colds but failed to prevent recurrence of the ear drainage." Colic was frequent the first two months of life, but not since the addition of multiple foods to the diet in the third month of life.

All oral and respiratory mucosa was pale on examination, and eosinofils were present in the nasal mucus. The left ear canal was filled with clear mucoid exudate. A diet limited to a few specific foods resulted in elimination of all symptoms. There had been no recurrence of the otitis media one year later.

Case 2.—H. R., a two-year-old boy, was seen January, 1952, with a history of year-round nasal drainage, frequent mouth breathing, recurring cervical adenopathy and repeated ear infections since one month old. The only remission of ear infections had been for a few months after x-ray therapy to the pharynx. A few attacks of colic were present during the first two months of life, and anorexia had been frequent since.

Examination revealed a pale pharynx with vascular injection, mildly pale nasal mucosa with many eosinofils in the mucus, and retracted ear drums. Tests for routinely ingested foods in early infancy revealed a large reaction only to orange. Omission of orange from the diet resulted in control of all symptoms, and prevented further ear infections.

Serous otitis media, or chronic secretory otitis media, is usually manifest by a fixed or moderately retracted drum which is reddish or amber in color, and usually without injection of the tympanic vessels. A fluid level may

*Case reports were added after the paper was presented.

be visible, as may air bubbles after tubal injection of air. Jordan[5] considered ninety-seven of one hundred eleven cases to be of allergic origin. Many cases of serous otitis media are probably due to the mucosa of the eustachian tube and middle ear acting as a shock organ. This may result from direct sensitization by a fluid such as milk repeatedly entering the tube and middle ear from improper bottle feeding in infancy. Without concomitant edema of the torus and eustachian tube, fluid in the middle ear would usually drain into the pharynx. Therefore, it is more practical to consider first the allergic factors producing edema and hypersecretion of the mucous membrane, rather than to ignore allergic causes and immediately treat by the use of older otologic measures such as myringotomy, tubal irradiation or adenoidectomy. Probably the effectiveness of these measures at times has resulted from the temporary suppression of allergic manifestations by surgery or trauma, as has so long been apparent in nasal therapy.

CASE REPORTS

Case 3.—L. C., a four-year-old boy, was seen January 28, 1953, with a history of intermittent decrease in hearing acuity, of occasional mouth breathing, of "not having been well all winter," and of attacks of "tonsillitis" in August and December, 1952.

Examination revealed pale facies, small jugulo-digastric lymph nodes bilaterally, pale pharyngeal and tonsillar surfaces, mildly hyperemic nasal mucosa with great numbers of eosinofils in the mucus, and mildly retracted ear drums. Tests of routine foods resulted in a large reaction to corn, a smaller reaction to bean, and minimal reactions to apple, chocolate and grape. Elimination of these foods was advised. Removal of the tonsils and adenoids was not recommended (an opinion being requested by the parents).

The patient was improved until a "head cold" two days prior to being seen February 6, 1953. Chocolate custard was eaten the day of onset. Examination was unchanged except for fewer eosinofils in the nasal mucus. Continued elimination of the questionable foods was advised, and Hista-Clopane® was prescribed.

He remained well until May 28, 1953, at which time paleness had been noticed two weeks, sore throat and intermittent fever several days, and decreased hearing acuity at times. To the parents' knowledge chocolate had been eaten several days previously and the day before, and corn two days before. Other children in the family and neighbors made an accurate knowledge of food consumption impossible, since corn products are so widely disseminated. Examination was again unchanged except for greater enlargement of the jugulo-digastric lymph nodes and paleness of the nasal mucosa.

One other attack occurred on November 11, 1953. All attacks were relieved by food omission and antihistamines, no other medicine ever being given. The mother recently reported that he has been quite well except on the rare occasion when chocolate or corn is eaten.

Case 4.—B. Z., a sixty-two-year-old man, was seen March 2, 1954, with a history of continuous ringing, roaring when talking, and mild ache in the left ear since a fire-cracker exploded in the lower part of a pay telephone booth while he was using it January 2, 1954. Previous history related only occasional nasal dryness and occasional frontal headaches.

Examination revealed a cloudy left drum and diminished acuity in the left ear. Later examinations revealed the left drum to be retracted and the presence of a fluid level behind it. Oral, pharyngeal and nasal mucosa showed vascular injection. The

torus around the opening of the left eustachian tube was pale and boggy, and produced pain in the left ear when touched. Only a few neutrofils were present in the nasal mucus. All symptoms were decreased temporarily by tubal inflation. Dramamine® and thiamin chloride eliminated the ache in the ear, but failed to improve the acuity or eliminate the roaring when talking.

Food tests were completed March 12, and reacting foods eliminated from the diet. All symptoms were decreased and the left drum appeared normal on March 16. A final examination on March 23, revealed identical acuity in both ears. The patient felt better, had an increased appetite and was gaining weight, and refused to add any eliminated food to his diet for specific trial.

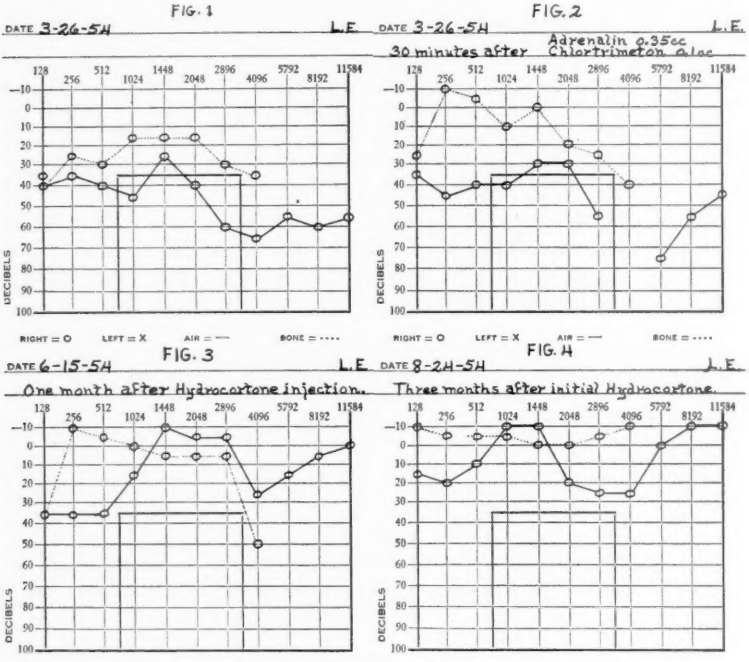
Otitis media with perforation exposes the muçous membrane of the middle ear to air-borne antigens in addition to antigens circulating in the system. Continuation of the perforation after control of infection may be due to allergic changes with the continued production of excess serous or mucoid secretion. Cases have been reported by Jordan[5] in which the secretion was more profuse following ingestion of foods to which the individual was sensitive. Often a pale, boggy mucosa resembling types of atopic rhinitis is visible through the perforation, and usually eosinofils are found on cytologic study. Aural polyps may occur in the same manner as nasal polyps, and usually recur similarly after removal unless the allergic background is investigated and corrected. Cholesteatoma has been found to occur more frequently in chronic middle ear conditions with an allergic picture. Healing of chronic perforations after closure with paper or cloth may in some cases result from the local suppression of allergy by trauma or by the elimination of air-borne allergens. Occasionally after endaural surgery, postoperative drainage due to allergy may occur from any remaining middle ear mucosa, or from an open eustachian tube.

INTERNAL EAR (LABYRINTH)

Endolymphatic hydrops, or Ménière's disease, is characterized by dilitation of the cochlea division of the membraneous labryinth, and secondarily of the saccule and utricle. Symptoms of deafness, tinnitus and vertigo are diagnostic, although Day[2] has found additional symptoms usually present. These are distortion of sound and hypersensitivity to loud sounds. The underlying pathologic change in these structures formed by ectodermal invagination is considered to be either allergy or dysfunction of the autonomic nervous system, resulting in vascular changes which produce angioedema initially in the cochlea duct. Laub[7] has reported two cases relieved by antihistaminic therapy, one of which was followed later by allergic evaluation and treatment with no recurrence, and with normal hearing acuity between attacks and after cessation. Derlacki[3] relieved two cases by omission of food factors and control of inhalant factors.

Decreased hearing acuity, particularly if variable, should be evaluated by an audiogram, followed by a second audiogram twenty to thirty minutes after medication. Kuhn[6] has recommended a small dose of epinephrine, and Armstrong[1] has advised a small dose of an injectable antihistamine.

Both consider improvement in acuity and in subjective feeling in the ears to warrant allergic evaluation and treatment in an attempt to maintain this potential improvement.



Figs. 1-4.

CASE REPORT

Case 5.—L. E., a twenty-six-year-old man, was examined April 11, 1953, with a history of gradual decrease in acuity in the right ear. Transient ringing was present in the ear after pistol firing. Past history included measles a few years before, but an absence of nose or throat symptoms. Examination revealed the nasal mucosa to be mildly hyperemic, and eosinofils were present in the mucus. The ear drums were negative, but the canals were dry and desquamating. Acuity for all tuning forks was diminished in the right ear and the Weber test was referred to the right. Treatment of the otitis externa, and oral aqueous Vitamin A and thiamin chloride at separate times resulted in no improvement. Food testing and elimination of reacting foods was also ineffective.

Therapy was discontinued until March, 1954, at which time there had been no noticeable change in hearing acuity during the intervening ten months. Examination revealed no change except retraction of the ear drums and vascular injection over the long process of the right malleus. An audiogram (Fig. 1) revealed mixed type hearing loss, right. Following injection of Chlor-trimeton® 10 mg and Adrenalin® chloride 0.1 cc, an audiogram (Fig. 2) showed marked improvement in acuity for low tones by bone conduction. Chlor-trimeton orally for five days resulted in greatly

improved acuity for 1448 and 2048 cycles by air conduction. A basic diet for one week resulted in no change. All of the above therapy resulted in no change in acuity in the right ear noticeable to the patient.

On May 14, 0.1 cc of hydrocortone acetate solution was injected into the right middle ear through the eustachian tube. All other therapy was discontinued. The patient then noticed steady improvement in acuity during the following two weeks, after which time the improved acuity remained constant. An audiogram (Fig. 3) on June 15, revealed normal bone conduction acuity except for the extreme cycles, and greatly improved air conduction acuity except in the low cycles. An additional injection of hydrocortone acetate solution was used, but resulted in no change in acuity noticeable to the patient. An audiogram (Fig. 4) two months after the second injection revealed normal perception and mild variation in conduction acuity. Since the initial improvement the patient has noticed no change or fluctuation in acuity in the right ear. An allergic mechanism appears to be present in this case, although efforts to determine it specifically have been unsuccessful.

At times tinnitus may be relieved by antihistamines, indicating the etiology. Although the cause or causes of otosclerosis are unknown, it appears to be the result of peripheral vascular changes which Wolff[8] believes may be chemical, vasomotor, allergic or trauma from vibratory phenomena.

MANAGEMENT

Preventive measures to minimize the frequency of sensitization should be considered during pediatric instructions relative to bottle feeding, and during otologic treatment by using medicines which are not prone to sensitize. Radical changes in diet should be avoided in ill as well as in healthy individuals.

Diagnosis of otologic allergy may be difficult, as acute phases are subject to spontaneous remissions. Often the entire constitution must be evaluated, including endocrine and psychosomatic or emotional factors. Therefore, a complete history is of basic importance, to be followed by a complete examination, both visual and cytological, and including bacterial or fungal cultures when indicated. Massive or moderate numbers of eosinofils in cytologic examination indicate allergy, but not the type of allergen. The finding of few eosinofils cytologically can at times be correlated with circulating antigen, in contradistinction to the massive eosinofilia produced by large amounts of antigen in contact with the outer surface of the mucous membrane. An absence of eosinofils does not rule out allergy, but leads to further consideration of other types of vasomotor conditions. Skin tests, when indicated, must be interpreted in relation to the entire history and clinical picture, and finally proven by therapeutic trial. Response to the use of antihistamines and to sympatheticomimetic drugs indicates the presence of allergic factors.

Treatment of an antigen-antibody reaction is simplest if exposure to the offending antigen can be eliminated. Temporary control can often be obtained by the use of antihistamines, or by histamine which helps to stabi-

lize the autonomic nervous system. Hyposensitization with vaccine may also give rapid improvement.

SUMMARY

An outline of aural conditions which may be entirely or partly of allergic origin has been presented.

Any ear condition not responding to customary otologic therapy, or continuing to recur frequently, should be further investigated from an allergic standpoint, even if this was also considered initially.

Allergic manifestations in the ear respond as completely and as rapidly to adequate allergic management as do those in other areas of the system.

Since hearing acuity is immediately or eventually diminished, it is essential that the otologist and allergist be capable of prompt and adequate recognition and management of these conditions.

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ANTIBIOTIC THERAPY IN UNDIAGNOSED UPPER RESPIRATORY INFECTIONS IN CHILDREN

Dr. L. M. Hardy, reporting in *The Bulletin of Northwestern University Medical School* (28:263, 1954), says that despite increasing incidence of allergic reactions and the knowledge that they have no effect on the virus of the common cold, promiscuous use of antibiotic and chemotherapeutic agents continues in the treatment of undiagnosed upper respiratory infections. He contends that "shot-in-the-dark" therapy may retard recovery. He studied 159 young patients with upper respiratory infections, dividing them into four groups. One group, as controls, received aspirin and placebo; another, Gantrisin® and aspirin; a third, oral penicillin and aspirin; and a fourth, Aureomycin® and aspirin. He found recovery to be more rapid in the control group than among the treated patients.

THE VALUE OF CHLOR-TRIMETON® IN THE MANAGEMENT OF ACUTE ALLERGIC AND FEBRILE REACTIONS TO BLOOD TRANSFUSION

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RECENTLY antihistaminic agents have been employed to prevent two of the most common immediate reactions to blood transfusion, namely, allergic and febrile reactions. If successful, as early reports appear to indicate,[1,4,5,6,8] the prophylactic use of an antihistamine could reduce the total incidence of transfusion reactions to less than one per cent. Other reactions, such as those caused by circulatory overload, mismatching, and isoimmunization, account for less than one per cent,[3] whereas the total reaction rate, including allergic and febrile reactions, has been reported to vary between 3 and 10 per cent.

Although the reported value of antihistamine prophylaxis of allergic transfusion reactions seems feasible, it is more difficult to accept its effectiveness in the prevention of febrile and/or pyrogenic reactions because antihistamines have no antipyretic action. Moreover, the causes of fever following transfusion are multiple, and difficult to differentiate.[10] Also, pyrogenic reactions are not dependent upon any specific hypersensitivity; in fact, they occur in both animals and man immediately after the first injection.[2] For these and other reasons, it was considered advisable to re-evaluate the effect of an antihistamine (Chlor-trimeton®) on the prevention of febrile and allergic type reactions to transfusions. Cases selected for study were classified as either normal or allergic on the basis of a few pertinent questions. This separation into allergic and non-allergic groups was made for two major purposes: First, it was felt that allergic persons should exhibit a relatively high incidence of allergic reactions, and therefore comparatively small groups of control and treated cases would suffice to provide the necessary information; second, it was considered that such a separation of cases could provide additional data from which a better evaluation might be made concerning the possible effectiveness of antihistamine in preventing febrile reactions in the same groups of patients.

From reviewing previous reports of transfusion reactions[1,3,4,5,6,8,10] and similar data from this hospital center, it is obvious that many more reactions must occur than are reported routinely. This situation exists because in many instances mild or asymptomatic reactions may be overlooked,

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such as those occurring in patients developing fever without chills, or urticaria without pruritus. Furthermore, febrile and allergic reactions may be masked in patients under the effects of anesthesia[9] and among patients simultaneously receiving sedatives or antipyretic drugs. Therefore, the patients selected for this study were limited mainly to medical cases in whom it was possible to obtain sufficient data before and after transfusion to make an adequate evaluation of the true incidence of both of these types of reactions.

MATERIALS AND SUPPLIES

The blood used was obtained from the American Red Cross, private laboratories, and from volunteer blood donors. In all instances it was collected in standard vacuum bottles containing ACD solution, and was obtained in accordance with accepted criteria for donors[10] and processed by techniques complying with national blood bank requirements. Transfusions were administered using pyrogen-free, disposable, plastic transfusion sets.

The Chlor-trimeton (Chlorprophenpyridamine Maleate) was supplied for intravenous use in ampules containing 10 mg/ml. by the Clinical Research Division of the Schering Corporation through the courtesy of George Babcock, Jr., M.D. Two procedures were used; the drug was either given intravenously prior to transfusion by injecting it directly into the tubing, or by mixing it with the blood immediately before its use.

PRELIMINARY STUDIES

Prior to investigating the prophylactic value of this agent, three pilot studies were made to determine independently its possible toxicity in the dosage recommended, and whether smaller doses might be equally effective. The first group consisted of twenty-one patients who were given pre-transfusion 2 mg doses. No reactions to the drug were encountered, but two patients had allergic reactions. In each of these cases, immediate injection of a 2 mg dose was effective. The dosage regime was increased to 4 mg and a larger group of 131 cases was treated. Again, no significant drug reactions were encountered, nor was there any appreciable beneficial effect. Therefore, a group of twenty-five normal patients was given the originally recommended dosage of 10 mg. Although nearly all of these patients had symptoms of mild drowsiness, they exhibited no other evidence of toxicity or intolerance, and had no febrile or allergic reactions.

EXPERIMENTAL PROCEDURES

Selection of Cases.—Alternate cases were given Chlor-trimeton or used for control purposes. All patients included in this study were selected on their ability to co-operate, and only if it appeared possible to obtain the necessary information. No cases used were given analgesic, hypnotic,

TABLE I. REPORTED INCIDENCE OF ALLERGIC AND FEBRILE REACTIONS FROM TRANSFUSION

Comparison with Findings at General Medical and Surgical Hospital

Series	Reactions Among Control Cases			Reactions Among Treated* Cases		
	Number Cases	Allergic	Febrile	Number Cases	Allergic	Febrile
Ferris	742	2.69%	4.3%	607*	0.16%	0.0%
Frankel	308	3.5%		284†	0.0%	0.35%
Offenkrantz	—	—	—	300†	0.0%	0.6%
DeGowan (1940)	2423	1.1%	2.9%	—	—	—
DeGowan (1945)	5386	0.8%	1.8%	—	—	—
Winter-Taplin	264	4.5%	6.8%	582†	1.37%	—
				445†	—	11.6%

*Pyribenzamine I. V. in 25 mg dosage mixed with blood prior to transfusion.
†Chlor-trimeton given I. V. or mixed with blood in 4 to 10 mg doses.

or antipyretic drugs for four hours before, during, or immediately after transfusion. Surgical cases under the effects of anesthesia were excluded.

Criteria for Immediate Febrile Reactions.—

1. Occurrence of a definite chill within the first four hours after transfusion.

2. A chill, or at least a 1° F. rise in oral temperature above a base line range of 98.6° to 99.6° F. within four hours.

3. Absence of a preceding febrile course or other condition which could account for chills or fever.

Protocol Use.—A written protocol was posted on all participating wards, and physicians and charge nurses were instructed regarding the information to be obtained and recorded on the special study forms supplied. The essential data included the patient's past history of allergy or reactions to previous drugs or transfusions, the amount of blood transfused, dosage of Chlor-trimeton given, type and severity of subjective and objective reactions, and a record of the patient's temperature immediately before and one and four hours after transfusion. One of the authors (C. C. W.) collected these records and personally verified all positive reactions immediately after they were reported.

The physician starting the transfusion obtained and recorded the patient's allergic background, and the nurse observed the patient's skin for such allergic manifestations as erythema, urticaria, edema, or other eruptions before transfusion and again each time the patient's temperature was taken. The observer also questioned the patient for symptoms such as chills, back pain, difficulty in breathing, generalized or local itching, nausea, vomiting, prostration, or any other unusual sensations such as dizziness or drowsiness.

If an immediate reaction occurred, the transfusion was stopped, a physician was called, and appropriate management was instituted. The Blood Bank was notified and routine investigations were made to determine the nature or cause of the reaction.

TABLE II. EFFECT OF PROPHYLACTIC USE OF CHLOR-TRIMETON ON THE INCIDENCE OF IMMEDIATE ALLERGIC AND FEBRILE BLOOD TRANSFUSION REACTIONS IN ALLERGIC AND NON-ALLERGIC INDIVIDUALS

Series	No. Cases	Dosage in Mg. Chlor-trimeton	Reactions in Allergic Individuals						Reactions in Non-Allergic Individuals						Reactions in Combined Allergic and Non-Allergic Individuals					
			No. Cases	Allergic		Febrile		Total		No. Cases	Allergic		Febrile		Total		No. Cases	Allergic		Febrile		Total	
				No.	%	No.	%	No.	%		No.	%	No.	%	No.	%		No.	%	No.	%	No.	%
A	264	None (Controls)	61	9	14.7	4	6.5	13	21.0	203	3	1.4	14	6.9	17	18.3	264	12	4.5	18	6.8	30	11.3
B	131	4*	27	3	11.0	4	14.8	7	25.9	104	0	0	6	5.7	6	5.7	131	3	2.3	10	7.6	13	10.0
C	101	10*	38	3	7.8	6	15.7	9	23.6	63	0	0	3	4.7	3	4.7	101	3	3.0	9	9.0	12	12.0
D	213	10†	40	0	0	6	15.0	6	15.0	173	0	0	27	15.6	27	15.6	213	0	0	33	15.4	33	15.4
	350	10†	66	1	1.5					284	1	0.35					350	2	0.57				

*Chlor-trimeton injected intravenously prior to transfusion.
†Chlor-trimeton mixed with each unit of blood.

RESULTS AND THEIR INTERPRETATION

Gross data presented in Table I give a comparison of the reported incidence of allergic and febrile reactions with the findings made in this study. As suspected, when a group of patients is examined critically for reactions, many more are found to have reactions than would be recorded by casual observation only, or by reviewing clinical records. The only reported series comparable to those studied by us is that of Ferris et al.[5] They found that antihistamine prophylaxis was effective for both allergic and febrile type transfusion reactions.

Several other groups of investigators have reported similar benefits.[1,6,8] In most of these studies, the bulk of the cases has consisted of patients undergoing major surgery; hence, under the reaction suppressant effect of general anesthesia. Thus, the low incidence of both kinds of reaction is not surprising.

Data shown in Table II present the incidence of febrile and allergic reactions in a total of 846 patients receiving whole blood transfusions from whom adequate information was available. Records from forty-two additional cases were excluded because of incomplete information.

Series A represents the control group and none of these 264 patients was given the antihistamine before or with the blood. There were sixty-one patients having definite allergic backgrounds and 203 apparently non-allergic individuals—an incidence of allergy somewhat higher than that in the general population. The striking finding in this control series is the tenfold higher rate of allergic reactions among the small group having allergic backgrounds versus that in the larger group having no apparent history of sensitivity. Of further interest, there is no significant difference in febrile reaction rates between allergic and non-allergic individuals. Finally, when control data for both types of patients are combined, the over-all frequency of febrile reactions (6.8 per cent) is not much higher than has been previously reported by Ferris[5] (Table I).

Series B represents a fairly large group (131 cases) given the drug in 4 mg doses just prior to transfusion. This dosage and intravenous method of prophylaxis has little if any significant effect on the rate of either type of reaction, although a 2 mg dose of the drug was shown to have definite therapeutic effect in several cases developing urticarial reactions in spite of the antihistamine prophylaxis.

In Series C, the drug was given intravenously in 10 mg. doses prior to transfusion. This series included an unusually high (38 per cent) percentage of patients having a history of allergy. However, only three of thirty-eight such individuals (7.8 per cent) had allergic type reactions. No similar reactions were encountered among the non-allergic group of this series. By comparison with the controls (Series A), it is seen that Chlortrimeton-treated allergic individuals have only about half as high an incidence of allergic type reactions as is found in similar untreated control

cases. The 9 per cent febrile reaction rate in this series is somewhat higher than in the control group (6.8 per cent). The majority of these febrile reactions occurred in allergic individuals.

Series D is comprised of two groups, but all cases were given Chlortrimeton (10 mg) mixed with the blood prior to its transfusion. In the first 213 cases, the incidence of allergic and febrile reactions was recorded. None of these patients had an allergic reaction. Therefore, the series was extended to 350 cases and allergic reactions were finally encountered in two instances. Temperature readings were not made in the latter group.

It is apparent from the data in Table II that when this antihistamine is mixed with the blood, and thereby administered more slowly than when given directly by vein or into the tubing, its effectiveness is greatly enhanced. The frequency of allergic type reactions among hypersensitive individuals is lower by a factor of about ten than in comparable controls.

The percentage of allergic reactions occurring in the non-allergic group of patients in this same series (D) of 350 cases is lower by a factor of about four than in similar untreated controls (See Series A).

Thus, it appears that either the technic (mixing) or the slower rate of drug injection is more important than the dosage used. The exact mechanisms involved cannot be determined from available information. A knowledge of blood levels of the drug following its injection when given directly by vein or after being mixed with the blood might give the answer. However, a satisfactory method for measuring microgram concentrations of the antihistamine is not available. At present the most plausible explanation is that when the drug is mixed with the blood and given slowly during the transfusion, effective blood and/or tissue concentrations are maintained longer than when the same dose is given rapidly prior to transfusion.

It is not unlikely that other factors are also involved, such as the possibility that a complexing between the drug and some component of the blood may take place, thus holding the active material in the blood stream or reducing its rate of excretion. This problem invites further investigation.

Again in this series (D) as well as in the controls (A), febrile reactions to transfusion occur with about equal frequency (15 per cent) among allergic and non-allergic groups of individuals. Thus it can be stated that that the antihistamine was totally ineffective in preventing febrile type transfusion reactions, even when 10 mg doses are mixed with each unit of blood prior to its transfusion. Furthermore, the 15.4 per cent incidence of febrile reactions in the group of 213 antihistamine-treated cases (Series D) is more than double that (6.8 per cent) found in 264 controls (Series A). The significance of this difference is not clear, but until more data have been obtained it is attributed to being within the limit of deviation inherent to this type of clinical study.

DISCUSSION AND RECOMMENDATIONS

The results of this study and their comparison with reported data on allergic and febrile transfusion reactions have provided considerable information of practical and theoretical value, and indicate the need and direction of future studies. It is most likely that the previously reported incidence of each of these two types of immediate transfusion reaction is entirely too low. Febrile reactions have probably been based on either the occurrence of symptoms (chills) or from routine clinical temperature records rather than according to measurements of body temperature taken at appropriate times after transfusion. Little effort has been made to differentiate febrile from pyrogenic reactions and most febrile reactions have been attributed to pyrogens.[3] Two other possible causes requiring further consideration are bacterial contamination and the presence of fragile erythrocytes, together with free hemoglobin[7] in blood samples stored longer than a few days. Furthermore, febrile and allergic reactions may be masked in patients undergoing major surgical procedures by the the anesthetic agent and also by drugs commonly employed to prepare such patients for general anesthesia.[9] Since the bulk of all blood being used in most hospitals with active surgical services is given either before or during operations, it is not surprising to find a low incidence of these reactions being recorded. Finally, unless data on minor transfusion reactions are collected by individuals directly interested in the problem, the information recorded is likely to be incomplete.

In our series, most surgical cases were excluded for two main reasons. First, it was considered hazardous to add antihistamines to the blood given to anesthetized patients who were simultaneously receiving other drugs having a hypnotic action. Second, complicated cases of this variety were not felt to be suitable for evaluating the prophylactic usefulness of Chlor-trimeton. The experience of others, nevertheless, indicates that the drug may be employed safely in such cases because no untoward reactions attributable to this agent have been noted. However, until further information is accumulated by careful observation of uncomplicated cases, we feel that the drug should not be used routinely in anesthetized patients. Certainly it should *not* be added to all the blood donor bottles which are prepared for patients receiving multiple transfusions during a single operative period.

Our data (Table II) indicate that the antihistamine prophylaxis is most effective when it is mixed with blood prior to its transfusion. The incidence of allergic type reactions is reduced to an insignificant figure, especially in groups of patients having a definite history of allergy. Therefore, in allergic individuals, who normally have a chance of one in six or one in seven of experiencing an immediate allergic reaction, the prophylactic use of this agent seems well justified. However, since allergic reactions occur in only about one case in one hundred untreated non-allergic individuals,

the routine prophylactic use of intravenous antihistamine in such patients hardly seems advisable or necessary. In our opinion, non-allergic individuals are better managed by using an antihistamine therapeutically when and if an allergic reaction occurs.

This study shows that Chlor-trimeton has no preventive action against the occurrence of febrile transfusion reactions in either allergic or non-allergic groups of patients. Moreover, febrile reactions occur more frequently than do those of allergic origin. Also, febrile reactions frequently cause considerable discomfort to the patient, and can be most disconcerting to the attending surgeon or physician. Furthermore, when severe chills and fever occur during or after transfusion, it is obligatory to determine whether these symptoms represent the prodromes of a serious hemolytic reaction. The latter type reaction has had in incidence of less than one per ten thousand cases in this hospital during the past seven years, where about eight thousand transfusions are completed per year, whereas moderately severe febrile reactions have occurred in about one to two cases per hundred. Thus, for every *bona fide* hemolytic reaction, a large number of cases must be processed to determine the true nature of such reactions. If one could eliminate or greatly reduce the frequency of febrile reactions of non-hemolytic origin, the technical load on the blood bank personnel would be lightened. The prophylactic use of antipyretic agents, which act on the temperature regulatory centers in the hypothalmus, might well accomplish this without interfering with other characteristic symptoms and signs of a serious hemolytic reaction. Thus, the use of an antihistamine plus an antipyretic should provide an effective and safe way to prevent both allergic and febrile type transfusion reactions.

An investigation of this type is now in progress, and it is anticipated that the oral administration of the drug plus acetylsalicylic acid one to two hours before transfusion should prevent nearly all acute allergic and febrile type reactions. Individuals reacting regardless of such prophylaxis should be given special attention, because their reactions are more likely to be of a serious nature.

PERTINENT CASE REPORTS

Several interesting incidents occurred which warrant reporting separately.

The first patient developed mild urticaria shortly after the start of a blood transfusion and was then given 2 mg of Chlor-trimeton intravenously. Twenty minutes later, even though the transfusion was continued, the urticaria had cleared.

The second patient, who had received a 2 mg prophylactic dose of the drug intravenously, developed mild urticaria within a few minutes after the blood was started. His urticarial reaction subsided in thirty minutes without stopping the transfusion, after a 2 mg intravenous dose was given therapeutically.

A third patient given 2 mg of the antihistamine intravenously, pretransfusion developed urticaria, asthma, and prostration, but was relieved rapidly by giving diphenhydramine intramuscularly.

The fourth patient, with known leukemia, developed a fleeting macular erythema twelve hours after a 10 mg intravenous dose of Chlor-trimeton had been administered pretransfusion. He recognized a similarity between this eruption and one he had developed about a year previously, when he was given an unknown antihistamine for an upper respiratory infection. Following a second 10 mg dose of the drug before another transfusion, he developed a similar skin reaction immediately which lasted many days. However, a skin biopsy of an affected area showed evidence for leukemia cutis.

A fifth patient, with Hodgkin's disease, was given 10 mg of the antihistamine mixed with one unit of blood, and developed an acute purpuric skin reaction with pruritus for the first time in his history. This dermatological condition cleared in four days while he was receiving tripelennamine therapy. The relationship, if any, between the acute purpuric skin lesions and the drug treatment could not be ascertained.

The sixth unusual case developed periorbital edema immediately after a transfusion where no antihistamine had been mixed with the blood. This acute allergic reaction cleared promptly after a 10 mg. dose of the drug given intravenously.

A seventh patient with proved Hodkgin's disease and a strongly allergic background was studied through nineteen consecutive blood transfusions. He had two allergic and one febrile reaction, when no antihistamine was given prophylactically. He developed two allergic and two febrile reactions when four mg of Chlor-trimeton were given intravenously before each of the next four transfusions. Then a Pel-Epstein febrile course developed. With each of the next seven transfusions, he received 10 mg doses of the drug intravenously before transfusion. Except for questionable febrile reactions and one mild allergic reaction, six out of seven of these transfusions were well tolerated. The last five transfusions were given with 10 mg doses of the drug mixed with each unit of blood. No reactions of any kind were observed.

Finally, after 300 cases where Chlor-trimeton had been given in 10 mg doses mixed with the blood, the first allergic reaction occured. This patient, with definite allergic background, developed a severe generalized urticaria. His transfusion was stopped after he had received only 300 cc. A 15 mg dose of the antihistamine was given intravenously, and the reaction subsided within twenty minutes.

SUMMARY AND CONCLUSIONS

1. A total of 846 patients was carefully selected from about 8,000 cases for inclusion in this study of immediate, non-hemolytic febrile and allergic type transfusion reactions in normal and allergic individuals.

2. In 264 untreated (control) cases, the incidence of immediate allergic reactions is about ten times higher among allergic individuals than in persons having no definite allergic background, whereas febrile reactions occur with about equal frequency in both types of cases.

3. Chlor-trimeton produced no allergic or febrile response when administered intravenously in 10 mg dosage to twenty-five normal individuals.

4. The intravenous administration of this drug in 10 mg. dosage just prior to transfusion is shown to reduce the frequency of allergic reactions by a factor of two when comparison is made with a similar group of individuals having positive allergic backgrounds.

5. If the antihistamine is mixed with the blood transfused, and thereby given more slowly, its prophylactic value is greatly enhanced. The incidence of allergic reactions is decreased by factors of about ten and four in allergic and non-allergic groups of patients, respectively. The greater effectiveness of this technique is tentatively being attributed to the slower rate of administration which may provide effective blood and/or tissue concentrations of the antihistamine for longer periods.

6. The drug was found to be totally ineffective when used to prevent febrile type transfusion reactions in either normal and/or allergic individuals.

7. No serious drug reactions were noted in any of the 451 cases wherein 10 mg doses of the antihistamine were given to patients who were also receiving blood transfusions; however, most patients admitted to mild drowsiness when questioned.

8. Small doses (2 to 4 mg) of Chlor-trimeton were found adequate and effective when given intravenously for the symptomatic treatment of immediate allergic type transfusion reactions.

9. The prophylactic use of antihistamines should be restricted to patients having a definite allergic background or a past history of allergic transfusion reactions.

10. Results of this investigation have led the authors to believe that the frequency of immediate allergic and febrile reactions to blood transfusion might be reduced to a minimum by administering antihistamine plus an antipyretic agent orally one to two hours before transfusion.

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MIDDLE-AGED MEN FACE GREATER HEART RISK, WOMEN LESS

The risk of dying from heart and blood vessel diseases has increased nearly 25 per cent among middle-aged men in the past generation, while the risk for women in the same age group has gone down by about the same amount. These opposite trends in the heart disease death rate of men and women between the ages of forty-five and sixty-five are the most striking piece of new information to be found in the 1954 revision of the statistical handbook, "Diseases of the Heart and Blood Vessels—Facts and Figures." The sixteen-page booklet was prepared by the American Heart Association in co-operation with the National Heart Institute of the U. S. Public Health Service to present basic facts essential to an understanding of heart and blood vessel diseases as a major health problem. The revised booklet, containing thirteen charts and interpretive text, brings up to date the original edition of May, 1952.

Dispelling a popular notion that heart and blood vessel diseases are necessarily associated with old age, the booklet reports that one-third of all deaths from cardiovascular disease occur under the age of sixty-five, and these diseases are responsible for more than one-quarter of the deaths from all causes in the twenty-five to forty-four age group. The newly revised booklet represents an attempt to provide a uniform picture of the complicated heart statistics by the chief voluntary agency concerned with this problem and the official government agency in the field. The booklet is being distributed by the American Heart Association and its affiliates primarily among professional people and those concerned with informing the public about heart disease.

ON THE USE OF IODIDE OF POTASSIUM IN ASTHMA

(Historical Document)

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For a year past I have looked through the various journals that came under my observation, in the expectation of seeing some notice of the subject of this article; but have, up to this time, met with but a mere incidental mention of the fact that hydriodate of potash has been employed with some benefit in asthma. I therefore send you the result of my experience with it, trusting that the statement which I make will excite the attention of our profession, and lead to a trial of the remedy on a more extensive scale. Some two years since, Professor Mutter, of Philadelphia, mentioned in the course of conversation with me, that he had accidentally discovered the fact to which I am now endeavoring to draw attention.

I immediately after this commenced its use with a number of patients suffering under this distressing and intractable complaint, and, to our mutual delight, they were all more or less speedily relieved. I have now made use of the medicine in some twenty-five or thirty cases of asthma, some of them very severe and aggravated; and so far, in no one instance where a fair trial has been made, has it failed to afford unequivocal and decided relief. These facts I have stated at our county medical meetings, and have urged the adoption of the practice upon many of our neighboring physicians; and so far as I can ascertain the result, all who have tried the remedy will endorse my statement of its value. I am happy to add the testimony of Dr. North, an eminent physician resident at Saratoga Springs, who informs me that he has experienced, in his own person great relief from the use of the medicine, and has witnessed the same effect in others. As a general rule, the patient is benefited after a few days' employment of the article, but some cases will require more time, perhaps weeks, before they improve; in one of mine, a very severe case of over twenty years' duration, I persevered for nearly three months before there was any decided amendment.

I feared, at the outset, that the medicine would prove to be merely a palliative (and even then it would be invaluable), but further experience warrants my belief that in mild cases of recent date a cure may be effected by its means.

In almost one fourth of my cases, relapses have occurred after discontinuing the remedy; this occurrence, however, was in most of them owing to severe attacks of catarrh, or to errors in diet and consequent derangement of the digestive organs, which, by the way, should never be overlooked in the treatment of asthma; I may mention in this connection, that most of my patients, while using this medicine, had an excellent appetite and gained flesh rapidly.

A long-continued use of the iodide of potassium will in some subjects occasion an eruption, generally of a pustular form (almost always ecthyma); and I have been twice disposed to attribute to it the occurrence of a slight conjunctivitis; the omission of the medicine for a few days, together with a few doses of rhubarb and soda, will be found sufficient

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for the removal of these inconveniences. It would scarcely be worth while to offer at the present time any explanation of the *modus operandi* of this medicine in asthma; nor is it necessary here to describe the symptoms, pathology, etc., of the disease, my sole object being to bring into notice what I have found a successful remedy for a distressing complaint. Extended experience must determine its value and applicability.

From two to five grains of the iodide of potassium, given three times a day, dissolved in water or some syrup, as for instance that of sarsaparilla or tolu, will generally be found sufficient for ordinary cases of the disease. Its continuance must be regulated by the circumstances of each case; of course no intelligent practitioner need be reminded of the attention requisite as regards diet, clothing and exercise. Dr. North stated that he had taken 3 ss. at a dose at bed-time, without inconvenience, and with the effect of preventing the paroxysm usually occurring at night.

Some of your readers may perhaps find fault with this paper, on account of its crudeness of style, and want of method and arrangement; but the practical physician, who will make fair trial of the remedy, will hardly be disposed to criticize the style of the article, or consider as wasted the time spent in its perusal.

Note—It may not be uninteresting or irrelevant to mention that I have given the hydriodate of potash to several horses troubled with the "heaves or hives" (I am doubtful as to its orthography), and in all, while under the influence of the medicine, the disease was suspended.—*N. York Jour. of Medicine.*

RESEARCHES ON SCROFULOUS DISEASES

(Historical Document)

Only two weeks since, the translation of this work was announced, and now it is on sale. This shows the activity of the press in a country where nothing is allowed to remain at rest. These researches are by J. G. A. Lugol, of the hospital of St. Louis, et cetera, Paris, a man of acute observation, who has seized upon everything that could render the origin or treatment of scrofula more certain. The translator, Dr. Doane, of New York, that miracle of bibliographical industry, says in the preface, that "the ravages of scrofula in different forms, the obscurity of its origin, and the uncertainty attending its treatment, will be acknowledged by every physican." He has not shackled the author with a burden of notes. At the close he has appended the most approved formula for different preparations of iodine, et cetra, for which practitioners will be much obliged.

Part I regards the inheritance of scrofulous disease and the health of parents of scrofulous children. This is subdivided into three chapters. Part II relates to pathological causes. Part III treats exclusively of external causes, under appropriate heads. There are some startling developments touching the vices of humanity in this work, and there are also practical suggestions of the highest importance. Published by J. S. Redfield, New York.

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Progress in Allergy

PROGRESS IN DERMATOLOGIC ALLERGY

Critique and Review of the Recent Literature

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NEW developments in the field of dermatologic allergy continue to make the subject a fascinating task to review. The recent widespread medical publicity given to hypersensitive reactions to penicillin and antibiotics as a group has helped to re-establish certain manifestations of allergic reactions in the thoughts of many allergically minded physicians. By the same token, practitioners who have concerned themselves but little with allergy (general surgeons and subspecialty surgeons) are now intensely interested in certain phases of drug and antibiotic allergy. Moreover, the more general use of the steroids—ACTH, cortisone, and hydrocortisone—as active therapeutic agents has added a certain luster to the therapeutic arm of the allergist.

In general, this review will follow the excellent plan established by Baer and Leider,[5] who have so ably prepared the annual survey of the literature in dermatologic allergy in previous years. Routine abstracting of all the literature in this field for the past eighteen months has not been attempted. Many articles have been selected because they demonstrate advances in our knowledge of fundamental principles of allergy or advances in management of problems in allergy. Some new and useful information is available. Some contributions are reviewed because they integrate new knowledge with old. The reviewer will avail himself of the privilege of comment on some of the work presented. An attempt has been made to avoid overlapping and repetition of material previously published in the reviews of the ANNALS.

ALLERGIC ECZEMATOUS CONTACT DERMATITIS

Experimental Studies.—There are a number of noteworthy contributions in the investigations of the site of antibody synthesis and transfer in contact dermatitis. Studies are in progress on the nature of the antigen and the response of the tissues under various measurable conditions. Baer, Serri, and Kirman[6] made attempts at passive transfer of allergic eczematous sensitivity in man by means of white cell suspensions. It is known that lymphocytes, monocytes and plasma cells are, if not actual producers, at least carriers of antibodies in the eczematous form of allergy. The demonstration of transfer of these antibodies, as reported by these authors, began with Landsteiner and Chase in 1942. These investigators were able at that time to transfer tuberculin-type and contact-type sensitivity in guinea pigs by means of suspensions of white cells from peritoneal exudates of sensitized animals. In 1947 Haxthausen confirmed these experiments on animals, using a lymphocyte suspension prepared from

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the thymus in guinea pigs. He failed to transfer passively eczematous sensitization in human beings by cell suspensions from lymph nodes. In 1949 H. S. Lawrence transferred tuberculin-type sensitivity passively and Baer and Sulzberger attempted to transfer allergic eczematous contact-type sensitization in man. This present method, reported by Baer and others, involved a new technique which avoided damage to the white cells either from repeated washings or from damage owing to high speed centrifugation. The method consisted in injecting plasma suspensions of viable white cells from sixty-six sensitive human donor subjects into sixty-six previously nonsensitive recipients. In retesting, it was found that three transfers were successful, one each to paraphenylenediamine, mercury and resorcin. This sensitivity persisted. In sixty-two patients, transfer was negative but in four active sensitization developed later.

It has been known for some time that the lymph node may be one of the sites of antibody synthesis. Studies on afferent and efferent vessels from lymph nodes after sensitization show measurable differences in the contents of the vessels. Haxthausen[55] used a lymphocytic suspension prepared from freshly-excised lymph nodes of subjects with eczematous eruptions. He obtained fine particles by a technique of preliminary chilling before the final production of the injectable material. This was injected intracutaneously into normal subjects. Retesting showed significant papular infiltration over control patients, which was considered a positive test. Patch tests were negative. The difficulties arising in this type of experimental work were discussed. The significance of his results are not fully established.

Epstein,[36] in a current review, discussed the background of experimental work which leads to our present knowledge of the antigen-antibody reaction in contact dermatitis. Considerable detail is given on the antigen, its action as a hapten and its conjugation with protein to form the final antigenic product. He described a number of clinical entities involving plant, drug and other contact dermatoses and noted that skin and mucous membrane sensitization may be separate and distinct. For example, poison ivy dermatitis is rarely encountered with mucous membrance involvement. By the same token, a patient may be allergic to a chemical agent in a vaginal suppository and show a negative patch test on the glabrous skin. The hapten-protein combination is termed a "protigen" and it is assumed that it would be different in the antibody derived from skin as distinct from the antibody derived from mucous membrane.

Nilzen[106,107] has currently continued certain experiments involving tissue reactivity and its behavior under certain hormonal influences. He previously had shown that in animals Compound E did not interfere with local tissue activity when injected intracutaneously or applied by inunction. Likewise, there was no reduction in skin reaction to primary irritants such as croton oil. In the present work adrenalectomy was performed on guinea pigs either before or after being sensitized with 2:4-dinitrochlorbenzene. Adequate controls were used. Following adrenalectomy, specific sensitization with 2:4-dinitrochlorbenzene and nonspecific (primary irritant) skin responses to croton oil were enhanced. Weaker solutions now produced reactions. It is suggested that the enhanced reactions seen after adrenalectomy were due to a weakened topical defense mechanism caused by lack of adrenocortical hormones. Nilzen also studied the effect of systemic stress and sensitization. This was accomplished by inducing stress in guinea pigs by exposure to cold and injections of formalin. He found that this depresses cutaneous sensitivity

to croton oil as well as specifically to 2:4-dinitrochlorbenzene. The anti-inflammatory action of increased cortico-adrenal steroids as a result of stress is the explanation for the depressing or inhibitory factor. In contradistinction, Guy[51] studied neurogenic effects in contact dermatitis by using guinea pigs previously sensitized to 2:4-dinitrochlorbenzene and subjecting them for five days to noise and electric shock stimuli severe enough to make them restless. The food and water intake was decreased sufficiently to produce weight loss. After five days of this treatment the animals showed a tendency to increased skin reactivity as demonstrated by patch test reactions to 2:4-dinitrochlorbenzene. Ten nonsensitized control animals were subjected to the same shock stimuli for five days and patch tested with the same antigen, and only one showed a positive skin response. It was concluded that under the conditions of this experiment, with guinea pigs so disturbed, the sensitivity of their skin was increased to contact agents.

An ingenious immunologic method was used by Seeberg.[145] This author devised a test using twelve subjects who were skin sensitive to streptomycin. The subject's serum was tested for its ability to agglutinate streptomycin-coated collodion particles. Normal controls were also used. He reported that most of the patients who had a streptomycin dermatitis showed high titers which fell when the eczema subsided.

Sulzberger, Witten and Zimmerman[169] studied the effects of oral cortisone acetate on patch test reactions to eczematous contact allergens. Five patients with known sensitivity to a number of eczematous contact allergens were given 150 mg of cortisone daily for five days. These patients were tested with various dilutions of their specific allergens before and during the oral administration of the drug. In only two of seven in this series was there a significant decrease in the level of sensitivity as shown by a diminution of response to patch tests during administration of cortisone. Diminished responses were noted for higher dilutions of some allergens. These findings suggest a regular but slight suppression of response to patch tests with higher dilutions but no suppression to standard test concentrations of contact agents. A practical conclusion from this study suggests that patients may be patch tested with standard dilutions while they are under cortisone therapy. It can also be concluded that if patients are exposed to the usual concentration of causal antigens, cortisone therapy will not materially aid in the control of the dermatitis. Although this is a small series, it confirms, in general, what is seen in daily clinical practice, namely, the allergen must be avoided if improvement is expected.

Grolnick[50] studied the effect of cortisone as a sensitizer of the human skin. Soon after cortisone ointment was available, it became apparent that some patients could not tolerate repeated applications of this preparation. The author used two techniques to determine the sensitizing ability of cortisone: 0.1 ml of cortisone containing 2.5 mg of the drug was used. One method consisted of repeated application of the drug by patch tests to the skin at spaced intervals hourly or daily. The second procedure consisted of repeated brief patch exposures with the drug made at short intervals to various parts of the body. Finally, a challenging test was made two weeks after the last application. The latter test was devised by Draize of the Department of Pharmacology, United States Food and Drug Administration. Twenty subjects were treated according to the first procedure and twenty-four subjects were treated by the second. Patients in the first group ranged from eighteen to sixty-three years of

age and most of these individuals had respiratory allergy. In the second group there were twenty-three unselected student nurses from seventeen to twenty-three years of age. In both groups the results in all subjects were negative and the author concluded that cortisone was not an active cutaneous sensitizer.

Mayer, as well as Baer, Sulzberger and others, has called our attention to cross sensitivities to the "para" group of chemicals. Rajka [121] studied twenty-three patients sensitive to chemically related compounds of the so-called "para" group, which includes various dyes used in coloring foods and fabrics, and numerous drugs, among them local anesthetic agents and sulfonamides. Reactions that would be expected on the basis of chemical structure did not necessarily follow. Thus, in patch test reactions, metol and hydroquinone were closely related, as were reactions to para-aminophenol and dimethyl-paraphenylenediamine. In certain instances it was thought that a chemical allergen produced reactions on the basis of hapten linkage to proteins, but in others this did not occur. The author concluded that patients allergic to the "para" groups should avoid sulfonamides, para-aminosalicyclic acid, para-aminobenzoic acid, procaine, and other drugs of the para-amino structure. It was also suggested that these patients should have patch testing before a clinical trial with any of these agents.

Hellerström, Thyresson[57] and others tested patients sensitive to turpentine with patch tests with purified terpenes, terpene oxidation products and chemical substances isolated from oxidized turpentine. Experiments showed that the intensity of the cutaneous reaction apparently ran parallel to the degree of oxidation of the terpenes, and that even persons hypersensitive to terpenes do not react to pure terpenes. A similar situation is seen in other forms of allergy; for example, patients may be sensitive to whole corn or peanuts but not sensitive to purified corn oil or peanut oil.

Schwartz[143] studied eczematous sensitization in various age groups, using a well known simple chemical substance, 2:4-dinitrochlorbenzene. He divided a total of 174 patients into three groups. In group I the ages were twenty-one to fifty-nine; in group II sixty to seventy-nine, and in group III, the patients were over eighty years. He concluded that the capacity for eczematous sensitization is not conspicuously altered with increasing age.

Pinkus[116] has compiled an excellent summary of the pathology in allergic dermatoses. Quoting Sulzberger, he stated that there are no organic changes, no tissue alterations which are in and of themselves pathognomonic of allergy, and almost every reaction based on allergy can be produced by a nonallergic mechanism. With the aid of two instructive diagrams, he shows the difference between tissue reaction based on epidermal response in acute and chronic eczematous contact-type dermatitis as well as the responses seen in the various whealing states. This paper is a realistic and common sense approach to tissue responses as they are found in allergic dermatoses and should be read in its original form.

Miescher[87] believes that he can differentiate by histologic means between primary irritation and allergic eczematous contact dermatitis. He reported the histology of eczematous processes which consist essentially of edema, spongiosis and vesiculation. The author favors edema as the primary element in the eczematous process. To differentiate the purely allergic from a simple toxic phenomenon he performed patch tests on intact but strongly hypersensitive skin with three different antigens. Biopsies performed six to twelve hours after contact showed a very vascular lym-

phocytic infiltrate around the subpapillary vessels. There were some areas of loosening of cell connections, and subcorneal vesicles were completely lacking. In the early state there was an influx of monocytic wandering cells, especially lymphocytes. A different picture was observed when primary irritants such as 50 per cent croton oil were used for patch tests. Biopsy after fourteen hours showed subcorneal, round or oval vesicles in which disintegrated epidermal cells were present. These findings suggest that the vesicle is caused by a toxic effect.

It has been shown by other authors that blister fluid taken from a fully developed primary irritant vesicle contained polymorphonuclear leukocytes, whereas those taken from vesicles of allergic eczematous reactions contained predominantly mononuclear cells. This would appear to agree with the findings of most experimentalists who believe that the mononuclear cells are concerned with the immunologic mechanisms in allergic eczematous contact dermatitis.

Clinical Studies.

The bulk of the articles which are of practical importance shows a heavy preponderance in two important fields of interest to the allergist and dermatologist. One is contact agents and experiences with these agents in the fields of new technology and new industrial processes. The second field is new and old drugs and reportable allergic reactions to them. Even though one has not developed an interest in the experimental side of contact dermatitis, the following reviews may be read with considerable profit.

Blank and Miller[11] studied a group of patients with dermatitis of the feet. It is very important in this situation to differentiate contact dermatitis, fungus infection with or without secondary bacterial involvement and many dermatoses which belong to or are part of other disease entities. These authors reported twenty-four cases of dermatitis of the feet caused by a component part of shoes. In each case a particular pair of shoes could be incriminated and positive patch reactions were obtained with portions of the shoes in all cases. Twenty-one of the twenty-four patients were women. Rubber adhesive was incriminated in a number of patients who had other rubber sensitivities,[92,93] at least by history. It is of interest that many of these patients had been treated elsewhere for fungus infections and other inflammatory skin conditions.

Schamberg and Flesch,[137] in dealing with a similar type of material, went further and determined the particular chemical in rubber which was responsible for at least some cases of sensitization. In their review they discussed most of the chemical preparations which go into the manufacture of rubber as it is used commercially. They discovered patients who were specifically allergic to thiobetanaphthol as a constituent of rubber. Several dozen related compounds were tested, with negative results. Although crossed sensitivity with certain chemical entities is an accepted concept in allergy, Baer, in a discussion of this article, emphasized the difficulty in establishing immunochemical relationships not only because of the nature of the antigens involved but also because of the differences in sensitivity spectra of different individuals.

The popularization of home cold wave permanents has resulted in a new interest in this process. Brunner[16] discussed medical aspects of home cold waving. The hair keratin is in the form of a polypeptide grid with a folded configuration which straightens out when tension is exerted

on the hair. Moistened hair stretches more readily. When the hair is dried in its new form it returns more slowly unless rewetted. This is the basis of temporary setting of the hair. The permanent set is produced by means of heat, alkalis or reducing agents. Chemicals most commonly used are borax, sulfites and thioglycolate salts. Home cold wave solutions are not primary irritants. Thioglycolate is applied at pH 9.5 and is a common offender. The neutralizer (sodium bromate) may also be incriminated. Gasser[47] also studied this problem and carried out patch tests with aqueous thioglycerin on thirty-two hairdressers suffering from acute or chronic dermatitis of the hands. Of these, 84 per cent showed a positive reaction to thioglycerin. Dermatitis of the scalp has not been observed in patients allergic to this chemical. Hairdressers who develop "beauticians' eczema" from cold wave materials must either use protective gloves and protective ointments, or change their occupation.

Further studies are presented by Sulzberger, Warshaw and Herrmann[167] with experiments in hypersensitivity to lanolin. They found that the relatively low incidence of reactions to patch tests with 5 per cent and 1 per cent dilutions of lanolin in olive oil, indicates that the intensity of lanolin hypersenstivity is weak when compared with other eczematous hypersensitivities. Patch tests with various fractions of lanolin showed that the allergenic material was present in the mixed alcohol fraction. It is suggested that more cases of lanolin hypersensitivity are not seen clinically because of the very low proportion of lanolin present in many commercial products available. Schwarzfeld[144] made patch tests to lanolin and aquaphor and found two out of ten patients sensitive to a factor common to both preparations. These patients had previously been suspected of having lanolin hypersensitivity. In the remaining eight patients, the sensitizer was distinct and different. Many patients therefore may be able to tolerate aquaphor even though they cannot use lanolin. Another agent found commonly in many ointment bases is propylene glycol. Warshaw and Herrmann[180] reported that undiluted propylene glycol produced positive patch test reactions in 138 (16 per cent) of 866 clinical patients with various allergic dermatoses. Of clinical interest is the fact that inflammatory responses were high during periods of low environmental temperature and humidity, and inflammatory responses were low or diminished during the hot and humid season. Distinct reduction in intensity of patch test responses was observed in two of three subjects tested after stimulation by exposure to heat.

The antihistaminic ointments have been widely used as agents to relieve pruritus and there has been a fair amount of literature describing reactions to some of these agents. Sidi, Melki and Longueville[153] reported 331 cases of dermatitis with these agents with positive skin test reactions. Thirty-seven were caused by antihistaminics and 30 per cent of these due to topical therapeutic agents containing antihistaminics. About 20 per cent of the cases were photosensitive. A percentage of this group were sensitive to phenergan which is widely used as a topical agent in France. It is of interest that in fourteen phenergan-positive cases, 64 per cent showed a positive reaction to paraphenylenediamine. It would seem that one can add this new excitant to the list of drugs in the "para" group. Tzanck, Sidi[176] and others recorded two cases of phenergan dermatitis with photosensitization. They stated that persons able to tolerate phenergan by mouth may become sensitized to it after local application of a phenergan ointment. Thereafter, even a minimal amount orally will precipitate an attack of acute dermatitis. Responses to other

antihistaminics may be negative. It is believed that photosensitization plays a role by the fact that the dermatitis appeared selectively on uncovered areas, such as the face, hands and arms.

Rostenberg, Bairstow and Luther[130] have considered that formaldehyde used in many institutions for sterilization of certain types of equipment presented a problem of eczematous hypersensitivity. They found that formaldehyde sensitivity of the eczematous variety was quite specific for each individual so exposed. In reading patch test reactions when using this agent, it was wise to wait for seventy-two hours or more because of the appearance of delayed reactions. The low sensitivity of the patient or the high dilution of the material tested was responsible for the delayed action. Formalin 10 per cent, is a potent eczematous sensitizer in their opinion and it should be avoided as a sterilizing agent in hospital use.

A report by Pirila[117] is concerned with sensitization to cobalt in pottery workers. The author recorded twelve positive reactions of 436 workers patch tested to 5 per cent cobalt nitrate. All had active cobalt dermatitis and all were exposed to wet clay. Relatively few cases of the dermatitis were observed when only finished wares were handled. Wet clays were the chief factors. The dermatitis occurs as an erythematous papulovesicular eruption on exposed areas. Morris[95] reported on dermatitis among office workers and also reviewed[101] what we know about cutting oil dermatitis. He related some interesting data in regard to dermatitis from water glass. This author[91] reported two patients who developed dermatitis from water glass (sodium silicate), used chiefly as an adhesive agent in paper corrugated cartons. Patch tests were negative. The clinical picture was so striking that he made further studies. These showed that patients were using an alkaline detergent. Mixtures of water glass and alkaline detergent led to positive skin reactions. Acid detergents mixed with the water glass gave negative patch tests and patients previously sensitized were able to continue in their employment using an acid detergent.

Dyes and mordants used in fabrics, foods and other industrial products have been the subject of many previous reports. They are intimately tied in with the history and development of eczematous dermatitis. Paraphenylenediamine dermatitis from fabrics is reported by Schwartz.[140-142] The current fashion in the popularity of ball point pens has resulted in a number of cases of contact dermatitis due to the dye, aminoazotoluene, found in the ink which is present in the red and green semisolid inks of the ball point pens and also in some shoe polishes. Meara and Martin-Scott[85] reported that this dye has a low sensitivity potential since they have found only three reportable cases thus far. In Great Britain 2,000 - 000 ball point pens are sold annually. Clinically, the patients present a dermatitis which is similar to that seen from azo dye sensitivity found in clothing, leather, foods, drugs, gasoline and many other materials.

An interesting and stubborn dermatitis of the palm was due to contact with toothpaste in a patient reported by Loewenthal.[78]. A forty-six-year-old woman complained of repeated attacks of itching, swelling, and vesicle formation on the left palm, of six months' duration. Physicians who have treated chronic low grade eczematous eruptions of the palms know how recalcitrant these eruptions may be unless the specific contactant is found. After long search, toothpaste was found to be the offending agent. The patient was edentulous and had worn full upper and lower dentures for a number of years. At least once a week, she cleaned thm thoroughly by gripping them in the palm of her left hand and scrubbing

them with a popular brand of toothpaste. After discontinuing this procedure, the eruption subsided and later a positive patch test was obtained with the specific toothpaste. The "baxin" component of the toothpaste was thought to be responsible for the dermatitis.

The eruptions caused by contact with various plant oils have always been of interest to allergists and dermatologists. Fromer and Burrage[44] reported their experience in the management of over thirty patients with a seasonal dermatitis on the exposed areas beginning in August and terminating with the frost. Most of the patients were males, outdoor workers over forty years of age. In untreated patients who have the eruption over five years, symptoms began earlier than August 15 and were often prolonged beyond the first killing frost. Patch tests were positive in all patients with a dilution of 1/100 ragweed oil, and comparable tests could be obtained with either the stem or leaf of the ragweed. At this patch test strength there were no false positives and no false negatives. Ragweed oil dermatitis is much more frequent in the middle Atlantic states and those states in which the raising of grain is a major activity. It can be a disabling dermatitis and to a farmer who is so afflicted it may be ruinous.

Although the oral treatment of ragweed oil dermatitis has been favored by some, this series of patients was given ragweed oil injections, using a perennial or year round method of treatment. The initial dose was 0.1 cc of 1:1000 dilution of ragweed oil dissolved in almond or olive oil. Increases were made of 0.1 to 0.2 cc weekly. Most patients could tolerate a dose from the 1:100 dilution and some patients could tolerate a dose from the 1:10 dilution. Patients were urged to follow the perennial treatment with a "booster" injection at monthly intervals using the same principles applying to the injection therapy for hay fever. The results of treatment in this series were comparable to results obtained in routine hay fever "desensitization." Of the patients treated 70 to 80 per cent showed good to excellent results, while 10 to 20 per cent obtained poor or moderate relief. Adjunct methods of treatment are antihistaminics, corticotropins and topical therapy.

Fisher[39] has followed this problem closely and reported immunologic phenomena in treatment and patch testing of ragweed oil dermatitis. He emphasized the point that patients should take a maintenance dose of ragweed oil for an indefinite period. Pruritus ani is one of the most persistent, annoying complications of oral hyposensitization and can be controlled by suitable adjustment of dosage. Urticaria, and other skin eruptions rarely occur if the dosage is increased carefully. The oleoresin is used for patch testing without the addition of any coloring matter since false positives are obtained if this is not avoided. Four of eighteen patients so treated showed a specific diminished reaction to patch tests following extended treatment. In the reviewer's series only 10 per cent of the patients can be shown to have either a diminished or negative patch test after treatment and this never occurs until the patient has had at least two or three years of continuous therapy at intervals of two to four weeks.

The importance of desensitization in eczematous contact-type dermatitis cannot be overemphasized in ragweed oil dermatitis. Most observers who have had experience with this type of treatment agree on the overall results. It represents one of the few situations in which the physician can offer some hope of hyposensitization in contact dermatitis, and may be the key that may lead us to similar treatment where avoidance of the antigen is not possible in other forms of eczematous dermatitis. Derma-

titis caused by trauma or allergy or both due to sawdust from industrial native woods is described by Weber.[181] Patch tests are not always helpful. The dermatitis may persist for years after exposure is terminated. Cookson and Lawton[25] reported hop dermatitis in Herefordshire. Hop dermatitis appears to be a true sensitization dermatitis of the skin which spontaneously clears when the patient is removed from the antigen. The antigen changes with aging since old hop oils produce negative patch tests. Dry hops, therefore, rarely produce this type of dermatitis.

Polunin[118] reported that all pineapple cutting laborers in canning factories in South Malaya show an abnormality of skin areas exposed to pineapple juice and to mild pressure. Contact with pineapple juice causes erythema of the skin, and over palmar skin creases, deep raw fissures may appear. Later the skin becomes white and opaque on the pressure areas. There is almost complete obliteration of the fingerprints over the fingertips. Experimental studies show that bromelin, a proteolytic enzyme in pineapple juice, is the cause of the dermatosis. Fingerprints return to their original pattern when the dermatitis subsides. Puglisi[119] distinguishes dermatoses in the fruit industry caused by lemon juice and by lemon oil (terpenes). He found that cheilitis, hyperpigmentation, angioneurotic edema, aphthous ulcers and papular or nodular eruptions may be the result of contact or ingestion of these antigens. Allergic dermatitis may occur in carpenters from contact with lemon wood in sawdust. A further report on plant world sensitization comes from Cohen and Reif[22] who reported on cutaneous sensitization to blue-green algae. A case is presented of a six-year-old girl who developed a recurrent seasonal (June, July and August) dermatitis on the exposed areas after bathing in a Pennsylvania lake. Patch tests were positive to lake sediment composed of a blue-green algae and further study led to the isolation of a substance, phycocyanin, the blue pigment found in this species of blue-green algae.

Eczematous dermatitis on the hands is one of the commonest of the superficial dermatoses seen in the office of the dermatologist. It should be of interest to the allergist as well. There have been contributions by Rowe and Flood and others which develop the food factor element in relation to hand eruptions. Rowe has implicated inhalants as a causation of hand eczematous lesions. There is no question that there may be many factors involved in hand eruption and these include contactants, atopy, food allergy, physical allergy, bacterial and fungous involvement, endocrine and psychosomatic elements.

Rowe's experience in "desensitization" of patients with hand eczemas using extremely high dilutions of antigen has not been accepted by most dermatologists. For several years Flood[40] has contributed to this subject, using his experience with elimination diets in the control of patients with dermatitis of the hands. He presents a practical outpatient approach to the problem. He does not believe that skin test reactions are criteria for the selection of foods, and his food elimination procedures do not entirely agree with the impression of most allergists as to the relative antigenic properties of most foods. In respiratory allergy, for example, chocolate, nuts and seeds are well known offending agents. This may not be so with hand eczema.

Futhermore, Flood believes that sensitization to foods may change with localities, depending on the popularity of certain foods and dishes common to a particular type of population. Food elimination and trial diets were used for several years in patients with hand eczema, with gratifying results in those who had had the gamut of dermatologic care which would

include superficial x-ray therapy. It is a very important aspect in the reviewer's opinion. Winkler[185] reported on the medicolegal aspects of hand dermatoses. Although many patients have an industrial problem it must be remembered that hobbies introduce new antigens which have no industrial connection and that some inflammatory hand dermatoses, such as psoriasis and neurodermatitis, may masquerade as an industrial problem.

In this connection, Gaul[48] has studied a number of patients with hand eczema and metal sensitivity. He found that the degree of sensitivity to soluble chrome compounds rested between 1:5000 and 1:20,000 in the test dilutions. This is much lower strength than that found for an organic mercurial preparation such as merthiolate or mercurochrome. In a series of sixty-eight cases of hand eczema, nickel showed the highest ratio of 4 plus reactions. In this series, females dominated 10:1 in metal sensitivity. The solubility of chromium compounds is a determinant in producing positive reactions. A patient sensitive to soluble chrome compounds need show no reaction to the insoluble compound or the metal itself. A dilution of 0.1 per cent or even 0.05 per cent is recommended for patch testing to avoid severe reactions. Excessive perspiration favors sensitization in industrial situations. For a time hand eczema was called housewive's eczema or soap and water dermatitis. Van Scott and Lyon[177] tested various commercial preparations of soaps for their effects on sulfhydryl groups in human keratin. The effect upon plantar keratin was most noticeable with detergents rather than the usual soap. Those preparations producing a greater alteration of keratin are not more likely to cause dermatitis of the contact type. Soaps are irritating to the skin in some individuals and under certain conditions they may also initiate, aggravate or prolong skin injury.

Seeberg[146] reported four cases of eczematous dermatitis from contact with or ingestion of beef, pork and mutton. Two patients suffered contact type allergic dermatitis as a result of handling meat during the course of their work. Patch tests with pork showed positive reactions and ingestion of pork and beef produced a vesiculopapular eruption in another patient. Patch tests with offending allergens were positive. The author reported that in all four patients positive tests were obtained only while the eczematous condition was active. It is of interest that repeat tests performed when the skin had cleared produced no reaction. The reviewer notes that this is a type of alteration of allergic sensitivity seen under certain other situations. For example, tuberculin tests which are positive in some forms of lymphoma of the skin, may become negative as soon as the skin condition clears. A negative tuberculin test in this situation is considered an anergic test.

Morris[99] has studied a large number of cases of questionable occupational etiology and, out of 2,000 dermatologic cases, 110 were found to be food handlers. In most of the cases there were eruptions on the hands and fingers, and they included dermatitis in candy makers, fish handlers, bakers, food handlers, waitresses, poultry dressers, vegetable clerks, and sausage workers. Less commonly involved were potato peelers, egg handlers and spinach handlers; two were finishers of chewing gum with positive patch tests to essential oils. This is of particular interest because the nonindustrial housewife who handles many identical foods in preparing the daily menu may actually have a hand dermatitis due to the foods and not to the commonly thought causes of soap and water and detergent preparations.

Two unusual contact reactions terminate this portion of our review.

One is by Rost[128] who reported allergic reactions to catgut preservatives. Sensitivity to mercurial derivatives used in the preservation of surgical catgut is the basis of this report. The history showed that on previous exposure to mercurial preparations, a generalized dermatitis had been noted by a patient. In the process of an appendectomy (avoiding mercurial skin preparations for disinfection), a medium chromic catgut was employed as a suture agent. Severe dermatitis appeared on the second postoperative day. Marked patch test sensitivity was demonstrated to phenyl mercuric acetate which was the solution contained in the catgut tubes. Control patch testing with the catgut was reported negative. Contact dermatitis due to the cord of a hearing aid was reported by Weil.[182] A single case of a patient with a lesion in the region of the ear and over the midportion of the clavicle is reported. A positive patch test was obtained with the synthetic cord, and covering the cord and ear piece with a coating of latex cured the condition.

An interesting article by Cruickshank[28] reminds us that the average industrial patient in a Birmingham, England, factory loses ten weeks work when involved in a skin industrial problem and 500,000 working days are lost annually from industrial dermatoses. A recent survey indicates that the high risk industries are in the rubber and leather fabricators as well as engineering tool setters, fitters and those employed in the management and maintenance of machine tools. These industrial workers are exposed heavily to various cutting fluids and coolants. Although electroplating, soldering, painting and spraying industries showed a high incidence of industrial dermatitis, there were fewer cases because there are fewer employes in this field. Making a special survey of the incriminating agents, excitants and allergens involved, Cruickshank found the oils and cutting fluids highest as causal agents; following these, chrome and plating solutions, then paraffin solvents and thinners, and finally sensitizing drugs used in minor surgery for industrial injuries.

Probably every allergist is familiar with Waldbott's[179] contributions to the study of allergic problems. For some time this author has been interested in a special study of the analysis of patterns of eczema in skin lesions of the eczematous contact dermatitis type. This analysis is used in addition to the history and patch tests as diagnostic aids. It is stated that a careful study of the eczematous pattern made on certain areas of the hands, for example, will help quite specifically in determining the etiologic agent or the mechanism or both, by which the dermatitis was acquired. An expansion of this study led to a current book, "Contact Dermatitis" (Charles C Thomas, Springfield, Illinois 1953). These test patterns are helpful in certain situations, especially in industrial dermatitis in a city such as Detroit where most of the material for this book originates.

In routine dermatologic practice the reviewer notes that test patterns are not so helpful because the patient usually has self-medicated the lesions or has seen a number of physicians for treatment so that the basic test pattern has become obscured. One must then rely on the memory of the patient in determining the original site of the eruption from a carefully taken history. This is not a very satisfactory procedure and is often misleading. However, if one is a plant physician and is familiar with the various technical procedures and materials used in a certain plant, test patterns become of paramount importance as a diagnostic aid. Foerster[41] summarized his experiences with industrial dermatoses and the original articles contain considerable detail and can be read with profit.

Morris[98] asks a provocative question in an article entitled, "Why doesn't the worker's skin clear up?" Twenty-four different causes of failure are listed which are responsible for failure of an industrial patient to recover after what has been deemed appropriate treatment for an industrial dermatitis. Over the past twelve years 3,000 cases of industrial skin disease have been reviewed, with the opinion that if a dermatitis does not clear after appropriate treatment there are other factors at work. These include contact factors at home, emotional factors, secondary bacterial infection, the intervening development of a fungous infection of the feet, physical extremes of excessive heat or excessive cold and a number of other exciting agents having to do with the routine of settling industrial compensation cases. This author[94] has reviewed his extensive experience with various types of patch tests. The nature of the materials used, the strength for normal and abnormal skins, and the technique of application are dealt with in some detail. Of special interest is the use of the Wood's light to help identify false negative reactions at the end of forty-eight hours, which become positive three to six days later. By means of the Wood's light, many of these reactions will be discovered on the day of removal of the test. Suskind[171] reported on allergic problems in modern industry, summarizing the various methods available to industry in evaluating the sensitizing potential and sensitizing index of new products. The author discusses in detail the bioassay method using guinea pigs or human beings in repetitive or prophetic patch test methods. These two widely used methods are subject to many variables in interpretation in the final responses. Particularly stressed are the ethylene amine class of compounds with the general formula $NH_2RNHRNH_2$ which are known to produce a high incidence of dermatitis from the standpoint of hypersensitivity. Beryllium, familiar to internists as an agent which produces a pulmonary picture similar to sarcoidosis, may also produce an eczematous contact dermatitis as well as cutaneous granulomas. Although new chemicals may replace old preparations, these latter substances must be retained in some instances even though they are sensitizers. Handlers of such chemicals as tetryl, TNT, plastics, plasticizers, dye intermediates, rubber antioxidants, accelerators and anti-mildewing agents, nickel and chromium products are all subject to sensitization. In spite of most careful animal and patch test studies, the usage test is still the most practical indication of the sensitizing potential of a new preparation or article of clothing to be introduced. For the workers, industrial hygienic programs must be instituted and carefully supervised. These include lectures on the materials handled, protective clothing, bland detergents, exhaust or other appliances to decrease air contamination, and skin protective agents.

Industrial dermatitis due to contact with brass is reported by Morris[90] who found five cases of proved brass dermatitis among 2,000 cases of industrial dermatitis. Brass contains approximately two parts copper and one part zinc with traces of arsenic, tin, lead, antimony and nickel. Patch tests with brass gave positive results in all five. The case reports show that when patch tests with the components of brass are done, reactions to one or more of the individual metals may be elicited. Morris[97] also reports dermatitis from waterless hand cleaners which have recently been introduced into industry. Nine cases of vesicular dermatitis of the hands are reported following the use of the so-called waterless type of handcleaners. Some of these preparations contain solvents of the naphtha series which are potent irritants and sensitizers. The author adds paren-

thetically that this type of cleanser is an expensive method of using kerosene.

Phosphorus sesquisulphide poisoning is reported by Burgess.[17] He reported the occurrence of dermatitis of the face, accompanied by itching, edema and erythema, in two women, the result of sensitivity to friction matches. Patch tests with the match tip and with phosphorus sesquisulphide were positive. Fumes of the burning match tips and direct contact of the fingers handling the match tips were responsible for the dermatitis. Phosphorus sesquisulphide is produced from red phosphorus.

Schwartz[141] reported on dermatitis in an industrial medical program and Skog and Thyresson[157] discussed the occupational significance of some common contact allergens. They studied the effect of simple chemicals such as chromium, nickel and simple organic preparations such as formalin and turpentine in 3,287 patients with eczema. They found positive patch test reactions to one or more of these agents in 32.5 per cent of men and 31.1 per cent of women. They concluded that sensitization to one or several of the agents mentioned in their tests is common among patients with eczema and dermatitis. This report would have been more helpful had they separated the reactions in certain classes of their patients. For example, it would be of interest in this large series to note the percentage of positive patch tests of these preparations in atopic dermatitis as compared with neurodermatitis, pyogenic and mycotic eczema as well as seborrheic dermatitis. The authors mentioned that in their initial 3,287 patients, the above classification of patients was made. The breakdown of figures, however, was not obtainable in this paper.

A voluminous literature on the use of local and systemic corticotropins has accumulated in the past few years in eczematous contact-type dermatitis. The enthusiasm in the early reports for these preparations in arthritis was matched equally in spirit in their use in bronchial asthma and eczematous states. Just as in rheumatoid arthritis the enthusiasm has now waned and it is the general impression that these hormones should be used in carefully selected cases. A frank, realistic and practical report on the use and abuse of cortisone and corticotropin in dermatology is presented by O'Leary.[110] In general, he advocates the use of these preparations in acute urticaria, drug eruptions, acute angioneurotic edema, contact dermatitis of severe degree and erythema multiforme. A number of serious or otherwise fatal conditions, such as pemphigus and systemic lupus erythematosus, also calls for the routine use of these preparations. He stated that in his experience the majority of skin diseases are not indications for the use of these hormones. The systemic use of the corticotropins calls for caution and observation for side actions. Wrong and Smith[187] reported in a similar fashion on the use of cortisone in the treatment of acute self-limited dermatoses. They discussed the results in thirty-two cases, with seventeen excellent results, eight considered to have a good response and seven a poor response. The cases included acute ivy dermatitis (Rhus radicans), acute contact dermatitis and dermatitis due to primary irritants as well as acute urticaria from penicillin and other drugs. One patient each had erythema multiforme, dermatitis medicamentosa due to phenobarbital, and serum sickness from tetanus antitoxin. One patient in this series died. This patient had a complicated hair dye dermatitis and required prolonged steroid therapy. A massive gastric hemorrhage during the course of therapy resulted in death. Schirmer[139] reported on the treatment of exfoliative dermatitis with cortisone and ACTH, and Hampton[58] discussed his experience with sixty patients

who had urticaria, allergic dermatitis and asthma treated with intravenous ACTH or the combined intravenous and intramuscular use of ACTH. The intravenous rather than the intramuscular mode of therapy with these hormones is favored. It is well known that the dosage of ACTH when given intravenously is only a fraction of that required when the hormone is given intramuscularly.

Sulzberger, Witten and Smith[168] reported on the local therapy with compound F hydrocortisone acetate ointment. This report is concerned with sixty-two selected dermatologic patients treated by local inunction of hydrocortisone acetate in various concentrations and in various ointment bases. Of these, thirty patients had atopic dermatitis. Six of the thirty were children. In twenty cases there was definite improvement, in seven no improvement and in three improvement was questionable. When improvement occurred it usually was seen in the first week of treatment and often in the first twenty-four to forty-eight hours. Maintenance of improvement was also noted during the entire period that the ointment was applied. The longest observation period was thirty-five weeks. In each instance when medication was discontinued, therapeutic effects usually wore off within four to five days. However, in a number of patients the improvement was prolonged and in some instances there were flare-ups even on continued use of the ointment. The authors pointed out that their findings are in contradistinction to the general lack of effect of cortisone acetate applied locally. They do not believe that there is any serious contraindication to the continued use of the 1 per cent ointment on small body areas up to about one-eighth of the total surface for periods as long as eight months. No toxic effects were noted in this series. In France a recent report by Sidi[154] confirms what is now well known to most dermatologists and allergists concerning the use of 1 to 2.5 per cent hydrocortisone acetate ointment. Forty-one patients with longstanding resistant dermatoses were treated by local application of 1 to 2.5 per cent hydrocortisone ointment. Striking relief lasting as long as twelve hours could be expected from a single application. Recurrences on omission of local treatment were common. Erythema of an eczematous eruption was rapidly reduced, followed by desquamation. Use of the ointment base without compound F on controls was ineffective. No toxic effect and no sensitization were noted in this series.

As with most newly introduced preparations one always asks the question, "When are we going to see sensitization with this preparation?" Zeligman[189] reported a case in a nurse who showed allergic symptoms after handling the hormone. Other causal allergens were eliminated by patch tests and history. Patch tests with beef corticotropin were negative, but patch tests with pork corticotropin were positive. Avoidance of the antigen was followed by relief of the dermatitis. S. de Seze[147] and others reported a number of cases of generalized urticaria after the prolonged use of cortisone therapy. These patients had no previous history of urticaria and the conditions for which they were treated did not in general show urticaria as one of the components. An unusually high incidence of allergic reactions was noted in patients in whom gold salts were used in conjunction with cortisone. In one case the administration of ACTH provoked the reappearance of urticaria which had cleared some days previously by administration of antihistaminics. An anaphylactoid reaction from ACTH is reported by Swift[172] The patient was a woman, aged thirty-five, who was treated for status asthmaticus. Her first treatments with ACTH were given in October, 1952. During the ragweed season

of 1953 she required twelve injections of ACTH. One hour after the last injection, giant hives occurred. Sometime later, tests were made as follows: positive reactions to ACTH pork aqueous; ACTH pork gel, and ACTH beef aqueous. The reactions were positive both to the pork and the beef components and this fact was verified by passive transfer tests on two patients.

There is no question that the addition of corticotropin in the treatment of patients with eczematous eruptions has been one of the most dramatic advances in recent years. Patients previously miserable and incapacitated, especially by pruritus of generalized eczematous eruptions, have been made at least moderately comfortable by the intermittent use of these preparations. There does not seem to be a well-controlled study to suggest that cortisone has any advantage over ACTH, or vice versa. The systemic use of the corticotropins should be limited to the diseases mentioned by O'Leary, and, to avoid complications, it should be used in short courses and rapidly discontinued. E. A. Brown and the reviewer saw a patient with ragweed hay fever and lesions of Weber-Christian disease (nonsuppurative panniculitis). She responded rapidly to cortisone and antibiotics and this represented the first remission that she had experienced in many months.

Although the allergist is mainly concerned with immunologic mechanisms in the management of allergic disease, it is a great relief at times to have adjunct methods of treatment available. These adjuncts or alternate methods may not even use immunologic principles, and an example of this is the administration of BAL in heavy metal sensitization. The BAL in this situation acts as a neutralizer or antagonist and actually interferes in the sulfhydryl groups or s—s linkages in the protein molecule. Cole[23] reported the frequency of chrome dermatitis in industry. After animal studies were first done, seven patients with chronic chrome dermatitis were treated with 3 per cent dimercaprol (BAL) ointment, with relief of symptoms even though they were continually exposed to chrome. This report needs further confirmation. If this method of treatment is successful on a large series of chrome-sensitive patients, it will prove invaluable in the field of industrial dermatoses from this widely used agent in industry. Kurtin and Orentreich[72] have used chelating agents to deactivate or neutralize the effect of the nickel ion which is a common sensitizer. Chelating agents have the ability to form soluble nonionizing stable complexes (chelates) with elements of the alkaline earth and heavy metal series. The authors have used this principle and note that the chelation of the nickel ion in solution will deactivate its antigenic ability to produce allergic eczematous reactions of hypersensitivity in cases in which the nickel patch test is positive. An active chelating agent applied in ointment form will inhibit the appearance of a positive nickel patch test applied over the ointment site. They do warn that chelating agents are not to be thought of as inhibitors of general cutaneous allergic reactions. This is a preliminary report and shows much promise.

This neutralization or inactivation principle is reported by Strauss[164] as well as by Barrett[7] using zirconium to inactivate the active principle urushiol found in various members of the Rhus or poison ivy-poison oak family. Apparently the element zirconium will inactivate urushiol *in vitro* and according to these reports it prevented the development of Rhus dermatitis in human volunteers if it were applied within a short time after the Rhus toxin came in contact with the skin. The cream contains 4 per cent zirconium hydrate and 2 per cent pyribenzamine hydrochloride

in a water soluble base and may also be used as a prophylactic agent against poison oak. Parish[115] described the use of diphenmethanil methylsulfate or Prantal® in the treatment of seventy-three patients with poison ivy dermatitis. Although the mechanism is not clearly understood, this anticholinergic preparation seems to block pruritus, especially in children, so that this symptom is minimized and there is less risk of secondary infection in patients with posion ivy dermatitis. Reyer[123] cited four patients who suffered an exacerbation of their Rhus dermatitis following antigen injections. Each injection of Rhus antigen appeared to produce a gradual and steady progression in the severity of the dermatitis. It is believed that each patient has an individual level of tolerance for the antigen. Most proponents of the injection form of therapy for poison ivy dermatitis have lost sight of the fact that the skin lesions are on a true contact basis and have never been proved to be on an accepted antigen-antibody foundation. The reviewer agrees with this author that poison ivy antigen should not be used during the course of an acute ivy dermatitis. Although many dermatologists believe that ivy desensitization is not even worth while, there is good evidence that allergists have been successful in the "desensitization" of patients with poison ivy susceptibility. Treatment, however, is given before the season as it is with hay fever, and many patients are, in fact, on a year round or perennial form of treatment, with one injection at the top level of dosage given at intervals of three weeks to a month. In the reviewer's experience, the aqua-ivy extract originally formulated by Spain and Strauss is the extract of choice, although many other preparations will probably be suitable. The entire subject of ivy desensitization needs more study by competent allergists, and it is my understanding that fairly extensive reports will be available soon on this subject.

Sanger[135] reported on the use of combined allergen-Chlor-trimeton® desensitization in highly sensitive patients. The combination of an injectable allergen together with an injectable antihistaminic has been used for some years. It seems to have a definite place in the management of the so-called "A" sensitive patient with pollinosis. Combinations of antihistaminics have now been used with other antigens, such as penicillin and ragweed oil, and there are reports that transfusion reactions may be minimized by the combination of one of the injectable antihistaminics at the time of transfusion. Vickers,[178] as well as Beerman,[9] has reviewed the subject of treatment of common skin disorders. Beerman is particularly anxious to warn against overtreatment in eczematous eruptions, and in this connection Lane,[74] in 1952, wrote an extensive article on overtreatment of dermatitis. The author recommends simple preparations such as Burow's solution diluted 1:16 or 1:20. Potassium permanganate or boric acid solution is also recommended. It is emphasized that absorption of boric acid in infants is a matter of much concern at the present time. The author believes that soaps should be avoided for cleansing purposes.

Various silicone protective creams to prevent the antigen from meeting the intact skin have been studied over the past two years. Smith, Day and Zimmerman[158] reported on studies of a nitrocellulose cream as a skin protectant against eczematous contact allergens. As a skin protectant, covicone has all the obvious advantages of a greaseless vanishing cream base plus protective efficiency before and after washing, as reported by these authors. The preparation is colorless when applied to the skin and a claim is made that no allergic sensitivities to covicone were encountered during the course of study.

The silicones consist of molecular chains of alternate oxygen and silicone atoms and differ from ordinary organic compounds in that certain carbon atoms are replaced by silicone atoms. The silicones are chemically inert and possess water repellent and adhesive properties. As is well known, many other preparations are now available in which the silicone formulation is used, and at the 1953 meeting of the Academy of Dermatology, in Chicago, three creams were mentioned, covicone, silicote and proderna. The reviewer has learned that the highway department of one of our Eastern states has used the latter product extensively over the summer of 1954 with gratifying results in the prevention of weed oil dermatitis. The reviewer believes that these protective agents will have limited value in preventing contact dermatitis. They may protect certain exposures and fail in others. They deserve a thorough trial.

Parish[114] reported on an effective method for the treatment of pruritus with the oral use of a combination of procaine hydrochloride and ascorbic acid. This is a follow-up of the intravenous use of procaine rather extensively reported in the last three or four years. Although there have been reports on the oral use of procaine as a relief measure for pruritus, this is the first report of a combination of procaine plus ascorbic acid. The reviewer feels that a large series of cases will determine the effectiveness of this treatment. Most readers are acquainted with a recent preparation which has been presented to allergists with a number of claims for general allergic treatment. Knight[67] discussed his experiences with Piromen® in the treatment of allergic disorders. This author concluded that although Piromen is not recommended as a substitute for routine allergic management, it seems to be of value in selected cases. Thirty-three patients suffering from poison oak dermatitis were treated with this agent by daily subcutaneous injections of 2 gamma of Piromen. The author claims good results in from two to eight injections which were needed for control. Lackenbacher[73] reported on the use of Chlor-trimeton maleate repeat action tablets in the relief of itching in various pruritic dermatoses. Two hundred thirty-three patients were studied. The author is impressed with the antipruritic effect of this long-acting agent over other antihistaminic drugs. There is an absence of side effects. The mode of action of relief of pruritus is not discussed.

Loewenthal[79] discussed the effects of sodium para-aminobenzoate in eczema and dermatitis. The author believes that there is a suppressive action on eczema and dermatitis, and this was studied in 200 patients. The dosage varied from 6 to 12 gm daily, administered orally in four divided doses for adults and proportionately less for children. One hundred sixty-five patients in this series improved and thirty-five showed no improvement. The best results were observed in atopic dermatitis and chronic disseminated dermatitis. Toxic effects of the drug included transient nausea, faintness, heartburn, and abdominal cramps. It is of interest that secondary infection occurred during the course of treatment and this was manifested by the appearance of impetigo and furunculosis, and in some cases tonsillitis developed during the course of therapy. Twenty-seven such patients required penicillin in addition to the agent under study. Sodium para-aminobenzoate has a growth-promoting effect on bacteria and this may account for the appearance of these bacterial complications.

Grayson and Steiner[49] likewise reported on sodium para-aminobenzoate and its use in twenty dermatological patients, eight of whom had atopic dermatitis. The medication was given orally for periods ranging from two weeks to several months and the daily dose was 16 gm in four

equally divided amounts. Only two of the eight patients with atopic dermatitis had good results. Temporary effect was noted in one other patient. It is suggested by these authors that "PABA" may be helpful in cases of therapy-resistant inflammatory or allergic dermatoses and that its parenteral route should be further investigated. The reviewer has not been impressed with the use of these agents in collagen disease (scleroderma, disseminated lupus erythematosus and dermatomyositis).

ATOPIC DERMATITIS

Although there have been a number of excellent contributions in the study of atopic dermatitis in the recent literature, it is novel and a little surprising to note one well-known dermatologist remarking that perhaps atopic dermatitis is not an allergic disease after all and another well known pediatric allergist remarking that atopic dermatitis in the infant is a capricious disease and after many years of study he wished that he knew more about it. Perhaps one can say that it is a constitutional disorder with allergic, dermatologic and psychosomatic aspects. Of great physiologic interest is the work of Shelley,[149-151] as well as Lobitz[77] and Sulzberger[170] and his group on studies of sweating. Shelley, corroborated by Lobitz, pointed out that the eccrine or sweat apparatus responds to different stimuli than the apocrine glands. If acetylcholine is injected into the skin intradermally it causes, in the normal patient, a local red reaction which appears first and is due to the direct vasodilatation effect of the drug. Secondly, there is an axon reflex flare around this red reaction and, thirdly, in some patients typical whealing appears. In the atopic, however, when acetylcholine is introduced into the skin, vasoconstriction occurs instead of the usual vasodilatation. Whealing appears in the injected site in 100 per cent of such cases. It is thought that the primary lesions that cause the intense pruritus in atopic persons are often cholinergic in origin, such as is seen in cholinergic urticaria, and that the secondary lichenification makes it difficult to see the urticarial lesions. It has long been known that atopic persons do not show the normal triple response of Lewis and Grant.[75] In these patients a paradoxic reaction takes place particularly when the disease is active. The initial red line appears briefly as in the normal response, but this seems to be immediately replaced by vasoconstriction of the same blood vessels producing the well-known white dermographism or blanch phenomenon. Lobitz[77] is of the opinion that this sign is of prognostic aid in that it is the first thing to appear on apparently normal skin when an exacerbation of the disease is beginning and the last sign to change to a normal triple response as the skin is healing.

In this same line of investigation Sulzberger, Herrmann and others[170] reported on the urticariogenic properties of human sweat. Sweat was obtained from subjects before and after exposure to specific allergens. The material was then pasteurized and shown to be sterile. Sweat was found to be urticariogenic in normal control subjects and in atopics. Sweat collected after deliberate allergenic exposures tended to be more urticariogenic for atopics than sweat collected without the donors' prior and deliberate exposure to allergens. Sweat was found to be more urticariogenic for subjects who showed positive skin reactions to other substances. This study supports the assertion that when sweat ducts are obstructed while labile acini continue to secrete, the sweat may be forced into the tissues. If then this material as shown by Sulzberger is urticariogenic, it accounts for the pruritic episodes which occur with periodicity in atopics.

Baer and Brauer,[4] as well as O'Leary,[109] have brought current thinking up to date in atopic dermatitis in recent contributions. O'Leary reviewed what is known about atopic dermatitis in the adult, and suggested that skin testing is unproductive of leads that cure atopy and that the psychogenic concept does not adequately explain the cause of atopy. Furthermore, he believes that psychoanalysis and profound psychotherapy do not give impressive results in the treatment of atopic dermatitis. Exacerbations of atopic dermatitis by physical agents are due to vasomotor instability in these patients and an improvement from a change in climate is due to a lying about and the "mañana" attitude, with lack of responsibility and freedom from daily duties. He found that fatigue, intercurrent infections, drugs and unpleasant mental situations are exacerbators of the disease and, further, that desensitization is worthless. The contributory but noncausal role of allergy in atopic dermatitis is discussed. A sensible approach to the functional aspect of the eczemas and atopic dermatitis is presented by Rothman.[133] Hill[58] concluded that the so-called protein allergens can and do excite or aggravate atopic dermatitis. One may or may not see an urticarial skin test reaction of significance. The wheal does not reproduce the lesion of atopic dermatitis. He postulated one or more additional factors, the so-called X factors, to be necessary. The wheal reaction is sometimes of diagnostic and etiologic significance because the whealing factor and the X factors often coexist. This agrees with Sulzberger's opinion that atopic dermatitis may not be primarily an allergic disease and the tendency for atopics to elicit the so-called white dermographism may be related to a cardinal local factor or Hill's X factor in atopic dermatitis. Other elements which influence the disease, including allergens, sweat difficulties, emotional and environmental distress, may merely precipitate the vasoconstriction which has been found in the skin by Lobitz,[77] Roth and others and which may be analogous to the bronchospasm of asthma.

In a turnabout fashion, Tuft and Heck[175] discussed their experiences with atopic dermatitis managed purely from the allergic aspect. Tuft, in particular, champions the allergic approach to atopic dermatitis using the entire spectrum of allergic investigations. This includes a painstaking history, skin tests with mature interpretation, trial diets and desensitization. As in former contributions by this author, it is to be noted that patients with atopic dermatitis who respond to this management are not numerous. The author has, however, been able to show that in selected individuals who are treated over an extensive period of time, the course of the disease has been favorably influenced by this approach. A patient, for example, whose atopic dermatitis is exacerbated from August to frost, should be given a trial with ragweed desensitization. Other inhalants fall into a like category for consideration.

Diamond[31] is in complete accord with this approach to atopic dermatitis. He emphasized the importance of inhalant allergens in the etiology of atopic dermatitis. Patients with dermal allergy frequently showed improvement coincident with treatment of the respiratory complaints by means of individualized desensitization series. Small doses used in desensitization were much better and caused less exacerbation than larger doses. The dermatitis can be exacerbated when the patient's tolerance is exceeded either by testing or when inhalant extracts are used for extended therapy. Ingram[60] believes that in patients with eczematous dermatoses, including atopic dermatitis, there is always a disturbance of emotional and nervous stability and adjustment as a primary cause, and he considers external causes such as irritants and allergens secondary to their

primary instability. The reviewer finds little to comfort him in an attempt to compromise these controversial opinions. If there is one field in which the clinician needs help, it is in the management of atopic dermatitis. These unfortunate patients often have a hostile and aggresive attitude which is frustrating to the physician. They are often unable to verbalize their problems and present at times a withdrawn, almost schizoid effect, which makes for a difficult time for the patient and the physician. Probably the best over-all results are obtained by using the best that the dermatologist, allergist and psychotherapeutist has to offer. The reviewer was recently presented with a problem of an adolescent sister and brother with atopic dermatitis of seventeen and eighteen years duration. This represented a lifetime of dermal disability. In this period of time they had seen well-known authorities in the field of dematology and allergy, and for the past two years had been under intensive psychiatric management elsewhere. Because the skin condition persisted to a point where it had interfered with their schooling, it was decided to give these two patients a trial at cathode ray therapy.[45] They had come from an eastern medical center for this therapy on advice of their dermatologist. Both patients improved considerably following their first course of cathode ray therapy. Psychiatric management has been discontinued and both are at college carrying a regular schedule of work. Cathode ray therapy is by no means the answer to the management of atopic dermatitis, but it should be considered for recalcitrant patients in whom all other therapy has failed.

Norrlind and Juhlin-Dannfelt[108] reported transepidermal penetration of lycopodium powder in a patient with atopic dermatitis. Severe pruritus at the site of application of the powder was produced within an hour. Urticarial wheals appeared in the cubital space above the site which later became scaly and definitely lichenified in forty-eight hours. This type of experiment again illustrates what Sulzberger has maintained for years. He has long thought that an atopic dermatitis may be primarily subclinical whealing and pruritus, and that lichenification, scaling and infiltration come as secondary features.

Sternberg and Zimmerman[162] studied stress situations in eczema, asthma and hay fever. The authors studied twenty-seven patients with classical atopic dermatitis and introduced stress factors which consisted in injections of epinephrine; one hour exposure in a room at 100 to 115° F. and 85 to 90 per cent humidity. The measure of the response was the eosinopenic index and lymphocyte-neutrophil ratio. Patients as well as controls responded normally to epinephrine injection by a fall in the eosinophil level. Lymphocyte-neutrophil ratio was also depressed by epinephrine. The atopics failed to show a significant depression in eosinophil count after exposure to the hot room. This was in strong contrast to normal subjects. This is considered to be a faulty alarm reaction and the authors believe that the defect in the alarm reaction may arise in the higher brain centers or in the adrenal medulla.

There are a number of interesting articles which deal with infantile eczema. The reader's attention is directed to the excellent review by Ratner[122] on pediatric allergy and the review by Halpin[52] on miscellaneous topics in allergy. Tachau[173] made a distinct differentiation between infantile eczema, seborrhea and intertriginous dermatitis in the infant. A description of classical infantile eczema and its complications is given. The author placed no reliance upon skin tests for the determination of true etiologic factors. It is emphasized that much can be accomplished

with topical therapy. Crude coal tar is perhaps the most valuable application, but it must be used with care. Antibiotics and antihistaminic agents are of limited use in the treatment of infantile eczema. The important features include the correction of environmental allergy or any maladjustments in the general health of the infant. Excellent results are obtained with radiotherapy. The reviewer agrees with this author except for the portion dealing with radiotherapy. Most dermatologists and radiologists would object strenuously to the treatment of infantile eczema with superficial x-rays. Brown and Holman[13] hospitalized nine patients with infantile eczema and atopic dermatitis for periods varying from twenty-three months to eleven years. All the patients had generalized eczema and all were given goat's milk as a substitute for cow's milk. This was done without preliminary skin testing. The authors did not find any effect on the course of the eczema by the substitution of goat's milk for cow's milk. It is admitted that goat's milk could be expected to benefit a patient with eczema only if the patient were sensitive to lactalbumin of cow's milk which is different from goat's milk. The casein fractions are similar in the two milks. It is generally known that patients with asthma and hay fever or atopic dermatitis in adolescent and young adult life give a history of infantile eczema. Purdy[120] obtained practically the same figures by simply taking ninety-three patients with infantile eczema who had been studied fifteen to twenty-one years earlier. He found that approximately 33 to 56 per cent of eczematous infants in this group were destined to many years or a lifetime of grave disability either from eczema or asthma, or both.

Steiner[159] reported a rare complication seen in atopic dermatitis. This author found glomerulonephritis in seven of forty-one patients with atopic dermatitis. In four of the seven cases the course of the glomerulonephritis and of the atopic dermatitis ran parallel. Urinary abnormalities could be correlated with the severity of the dermatitis in many instances. Nothing is said about secondary infection which may have coexisted at the time of the atopic dermatitis. In spite of these findings, the reviewer, who has hospitalized hundreds of patients with atopic dermatitis over the last two decades, cannot recall a single case of glomerulonephritis so encountered during the routine course of hospitalization. If the atopic dermatitis is severely impetiginized, however, glomerulonephritis is a distinct possibility.

Halpin[52] commented, in his review article on miscellaneous topics in allergy, that any child with atopic eczema should not receive smallpox vaccination during the time that lesions of any consquence are in evidence. The lesions should first be cleared with proper management. Then, during an interval of freedom from skin lesions, vaccination for smallpox can be completed.

Fontana[42] noted that no one aspect is all-important in the treatment of infantile eczema. He is interested, like Ratner, in prevention of infantile eczema, and makes the point that food should be added to the infant's diet with caution and food mixtures should be avoided. The initial serving of any new food to a susceptible infant should be small.

Nelson and Stoesser[105] have long been interested in the problem of infantile eczema and have made two contributions. One is a study of cleansing agents in infantile eczema. They are of the opinion that much of the irritation caused by soap has been ascribed to its alkalinity. This produces swelling of the horny layer of the epithelium, as well as the partial debridement of this layer. In those patients who complain of irri-

tation of the skin by soap, the only solution is the substitution of a non-irritating cleanser for both toilet and general household use. They believe that synthetic detergents of certain types may solve the problem. These are surface-active organic compounds containing hydrophilic and hydrophobic groups. An extended trial with Lowilla® cake was found to be most valuable in the therapy of infantile eczema and patients in whom soap irritation is a problem. These authors[163] also were interested in the problem of vitamin A therapy in patients with dry and ichthyotic types of skin among infants. Synthetic vitamin A was found to be of value in this type of skin complaint which often underlies or precedes infantile eczema. The dosage varied from 25,000 to 200,000 units daily in children six months to ten years of age. The medication was used for periods of from three to twenty-one months. Three of nine patients showed moderate improvement, while six showed marked improvement.

Owings and Riley[113] studied the electrolyte levels in the serum of infants in the first two years of life during the exudative phase of infantile eczema. Elevations of the serum sodium in some and of the serum potassium and phosphorus levels in others are reported. With improvement of the eczema the electrolyte levels tended to revert to normal. The authors suggest that these changes may represent potassium and phosphorus mobilization and loss, with sodium retention and subsequent water logging of the shock organ. The reviewer notes that there may be so many other factors which upset electrolyte imbalance that it would be hazardous to draw any specific conclusions from these findings. Perhaps if the authors could follow these patients for a suitable length of time when they are in complete remission, then duplicate the findings when the infants were in the exudative state, and show a complete reversal during a remission, the findings would be of some significance. It is true that eczematous skin appears waterlogged and the cells show intracellular and intercellular edema or spongiosis. The administration of a salt-free diet or the administration of diuretics, or both, in adults does not appreciably alter the course of an exudative dermatitis. It would be of great interest if these findings could be duplicated in adults.

Rosenthal[127] discussed the neuropsychiatric aspects of infantile eczema, with special reference to the role of cutaneous pain receptors. This appears to be a purely mechanistic approach. The author believes that non-allergic infantile eczema may be thought of as an attempt by the infant to shield the most sensitive, exposed portions of the skin from real or anticipated injury and correspondingly from unpleasant external stimuli. He presents a mechanistic, nonimmunologic approach involving destruction of prickle cells in the epidermis with transmission of retrograde stimuli passing along pain fibers to terminals immediately adjacent to these prickle cells. The author believes that this leads to necrosis and the spillage of cell contents into the tissue fluid, which increases osmotic pressure locally and sucks adjacent tissue fluid to the areas. Increased spongiosis then mechanically forms the intra-epidermal vesicles.

In discussing this paper, Sulzberger[166] stated that the claim that there is a lack of soothing skin experiences in these infants sounds fantastic, since he cannot conceive that there are certain families in which generation after generation of mothers fail to give their babies "soothing skin experience." In this connection, Frumess[46] discusses the role of the emotions in dermatoses in a more realistic and clinical manner as it is seen by the dermatologist. This article, together with the article by Rothman,[133]

previously quoted, seems to be an acceptable approach to this phase of the study and management of atopic dermatitis.

Hill[59] has had an extensive experience in the management of infantile eczema with oral cortisone. It is his opinion that treatment with cortisone by mouth has a very definite place in infantile eczema. Short term therapy with large doses is of little practical value except for periods of extreme emergency, but long term therapy with smaller doses is a worth-while procedure in certain cases. If eczema is entirely controlled with 75 mg or less, cortisone should be continued at this level. If this dose does not alter the course of infantile eczema, larger amounts should not be used. The beginning dose is 75 mg of cortisone daily and as soon as eczema is controlled, the dose is reduced by 12.5 mg each day to reach a daily maintenance dose for that particular patient.

It is emphasized that cortisone is only symptomatic treatment and Hill also stressed what is well known, that during the course of treatment if a surgical operation or other medical emergency occurs, it is necessary to increase the cortisone at least 50 per cent before and for several days after the emergency. When cortisone is discontinued, it should not be done abruptly. It is apparently possible to continue giving cortisone over many months without apparent harm to the child as far as metabolic and growth factors are concerned. While this study is a necessary and important part of clinical research, the reviewer believes that this mode of therapy, using cortisone over long periods of time, had best be left in the hands of experts in large medical centers.

URTICARIA

In the last review on progress in dermatologic allergy Baer and Leider[5,6] were justly critical of the type of investigation presented in this field. They reported the lack of rigidly controlled studies and "the most absurd therapeutic claims" with respect to urticaria. Fundamental advances in our knowledge of this disturbance are lacking. While the capillary may be structurally at fault, immunologic, enzymatic, electrolytic and other mechanisms should give us more insight into this troublesome condition. A number of ingenious experiments on direct visualization of the capillary and its contents under various experimental conditions have recently been reported. These studies represent a refinement of the old "moat" experiments in anaphylaxis, presented about a decade ago. Irwin and Burrage[61] stated that there has been a tendency to move the research laboratory nearer to the patient. They reported[18] on microscopic observations of the intrahepatic circulation of living guinea pigs before and during anaphylaxis.

The Knisely method was employed using a quartz rod to carry transillumination of living tissue so that small blood vessels of internal organs could be studied directly with microscopes. During anaphylaxis leading to death, the intralobular hepatic vessels underwent several interesting changes. The sphincters of the sinusoids at the central venule shut off. The hepatic arterioles contracted and linear blood flow in the central venules stopped. The sinusoids became engorged with blood, and linear blood flow in the portal venules ceased. No open hepatic arterioles were found during anaphylaxis. A considerable amount of blood accumulated in the liver, confirming the gross appearance of this organ. These investigators are continuing their studies of the blood vessels of the bulbar conjunctiva of human patients with allergic disease. Observations on patients with severe asthma before, during, and after cortisone therapy indicate

that arterioles constrict, venules are dilated and the red blood cells form into aggregates which are more predominant on the venous side during cortisone therapy. Further investigations along these lines in patients with urticaria and angioneurotic edema would be of interest.

Using a similar technique, Shulman, Fulton and others[152,188] studied capillary activity by direct microscopic visualization of the mucous membrane of the everted hamster cheek pouch. In the living animal, it is possible to study capillary physiology under various experimental conditions. These animals can be sensitized and shocked and the effect noted. In addition, the effect on the capillary by various agents may be noted. The effect of toxins such as moccasin venom, physical agents such as x-rays, and injury and recovery due to burns may be carefully studied. Petechial formation in the cheek pouch of the hamster was studied by Lutz and others[81,82] who reported capillary responses following topical application of filtrates of Streptococcus hemolyticus, nonbacterial inflammatory agents such as formaldehyde, turpentine, croton oil and mustard oil, and many other forms of trauma. Susceptibility to petechial formation induced by negative pressure was increased during twelve to seventy-two hours after total body irradiation (1,000 r to 1,500 r). Susceptibility to petechial formation was decreased after subcutaneous administration of cortisone. It would appear to the reviewer that fundamental studies of this type are critically needed in our efforts to understand the underlying pathologic physiology which occurs in urticaria. Although petechiae which represent clinical purpura are almost the end stage of capillary collapse, intermediary damage which produces transudation of the nonformed elements of the blood, resulting in whealing or urticaria, is another logical avenue for experimental study.

Samter and others[134] studied a series of twenty-four patients sensitive to aspirin whose symptoms were either angioneurotic edema or asthma. In their experience, allergic symptoms following aspirin appeared three to four hours after the administration of the drug. Most allergists would agree that reactions to aspirin, particularly those resulting in edema of the mucous membrane, may be seen within seconds or minutes after exposure to acetylsalicylic acid. Urticaria following tetanus toxoid is discussed editorially.[34] Edsall of the Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C., reports a sensitivity to this agent. Even though small amounts of antigen are used, serious generalized reactions may occur in patients who are hypersensitive. Should there be any indication in the future to use tetanus toxoid in such a sensitive patient, a skin test with fluid toxoid diluted 1:100 or higher should be done. Before undertaking additional immunization it would be desirable to obtain a toxoid which is not produced on a potentially allergenic medium, since most patients are sensitive to the constituents in the media rather than to the toxoid. During World War II the reviewer was responsible for the supervision of thousands of injections of tetanus toxoid administered at a large army induction center. Urticaria, angioedema and purpura were not uncommon complications of this procedure. It was found advisable to skin test all inductees who had a past history of allergy. Reactions were largely eliminated in hypersensitive patients by giving the prescribed amount of toxoid over a twenty-four-hour period in small increments. It should also be kept in mind that intradermal rather than subcutaneous desensitization is possible and, while this procedure does not have official recognition, there is adequate clinical and experimental data to support intradermal immunization with typhoid and other antigens.

Urticaria due to the digitalis series is rare. Wolfe and Geiger[186] reported an eighty-two-year-old woman with congestive heart failure who developed urticaria following the administration of each of a number of digitalis preparations which included whole leaf digitalis, digitoxin, digoxin, digilanid, lanatoside and squill glycoside. The patient also developed an enanthem interpreted as an allergic cystitis, which was examined by cystoscopy. This disappeared when the digitalis was stopped. There was no associated eosinophilia. Scratch and patch tests with digitalis products gave negative reactions. The author did not mention any substitute preparation to control the patient's cardiac symptoms. Morgan[88] reviewed what is known on cholinergenic urticaria beginning with the studies of Grant, Pearson and Comeau. This is a good review article but adds nothing new to our knowledge of skin hypersensitivity to acetylcholine. A worthwhile review on cold urticaria and purpura as allergic aspects of cryoglobulinemia is presented by Steinhardt and Fisher.[160] Patients with this condition have previously been described with Raynaud's syndrome, cold urticaria and purpuric manifestations. The term was first used by Lerner and Watson in 1947 to designate the presence in the blood of a cold precipitable serum globulin which dissolved upon warming. The authors presented a case report of a patient who had cold urticaria since 1948. Purpura of the lower extremities was noted about February 1951. Selected intradermal tests showed 3 plus reactions to dust, milk, wheat and coffee. However, when the patient was given ergotamine tartrate for migraine, extensive purpura recurred on both upper and lower extremities. Laboratory studies, including platelet count, sternal puncture, and liver function tests were normal. Sedimentation rate, Westergran, was 88 mm per hour corrected. Total blood protein was 10.7 gm, albumin 4.1 gm, globulin 2.3 gm, and cryoglobulin 4.3 gm. The suspicion of cryoglobulinemia was aroused by the presence of a gel-like appearance of the blood, the high sedimentation rate in the absence of infection or neoplasm and the associated cold urticaria and purpura. Passive transfer to cold could not be accomplished in this case of cold urticaria in ten donors' skins. Intravenous benadryl, 50 mg dose, caused a reduction in the size and duration of the urticarial wheal upon subsequent exposure to cold. Simultaneous administration of ACTH and cortisone did not change the intensity, duration or size of the wheal formation. A refractory period of seventy-two hours' duration occurred after inducing a wheal by cold exposure on this patient.

Twenty-eight hospitalized patients with severe acute urticaria, six patients with chronic urticaria and ten patients with acute dermatitis venenata received a single day course of ACTH as reported by Ekblad.[35] Subsequent courses of the illness in some patients were treated with cortisone. In general, ACTH was more effective in acute urticaria than cortisone in the doses used. The relief of symptoms on such short term treatment was an unsatisfactory experience and it would seem that a more extended use of the hormone, tapering off rapidly, would be more desirable. Canseco and Salinas[19] reported favorably on the use of aminophylline in the management of allergic urticaria. The pharmacodynamics of this drug in the symptomatic control of urticaria is reviewed.

Papular urticaria is reported by Rook and others.[125] The cause is now considered to be parasitic sensitivity rather than food allergy. The authors noted improvement upon hospitalizing their patients. The suggestion was made that fleas or bedbugs had been removed from the environment of

the sensitive patient. No benefits were derived from antihistaminic preparations in papular urticaria.

DRUG ERUPTIONS

Perhaps the greatest interest in the past few years by the profession at large has been directed toward new drugs and the untoward reactions that may develop from their use. In sifting the recent literature on drug eruptions, one is impressed by the preponderance of contributions revolving around the use of the antibiotics and penicillin in particular. The entire subject of penicillin reactions, which includes the skin and visceral manifestations of hypersensitivity, is reviewed by Kern and Wimberley.[62] They believe that all patients with a previous history of hypersensitivity to penicillin should be scratch tested with penicillin if its use is again anticipated. If the scratch test is negative, they recommend an intradermal test with 5,000 units per cubic centimeter. Delayed reactions are interpreted as milder clinical symptoms. Negative skin tests do not rule out the possibility of ensuing reactions. The risk, they believe, is much less. It is suggested that all unnecessary use of penicillin be stopped and they also recommend the avoidance of depot penicillin. Penicillin by mouth is less sensitizing and should be used whenever possible. It is also suggested that one should avoid giving penicillin in combination with another drug when administering the preparation parenterally.

Rostenberg and Webster[132] have reviewed the most frequently seen reactions to antibiotics. These include:

1. The urticarial or serum sickness type with manifestations of multiple erythema, angioneurotic edema or purpura and is usually accompanied by constitutional symptoms. The incubation period is from a few to many days and it is believed that the parenteral use of the drug increases the likelihood of allergic sensitization. Depot penicillin probably favors the development of sensitization over the aqueous type. Penicillin acts as a hapten and conjugates with a body protein to yield the complete antigen.

2. Erythema of the ninth day: various toxic eruptions may occur in this disturbance with or without constitutional symptoms. Some patients may continue the treatment in smaller doses. This is explained as true Milian's biotropism or ecologic interference.

3. The "id" type of reaction: various eczematoid eruptions of the feet, hands and groin are seen. It is rarely associated with constitutional symptoms. The onset is early in the course of treatment and usually within twenty-four hours. Continued treatment intensifies the condition. There may be an antecedent history of dermatophytosis. The mechanism is obscure, but many of these patients have delayed tuberculin type reactions to penicillin. This type of sensitivity can be shown in patients who have never had penicillin previously. Does Trichophyton elaborate a penicillin-like substance? Most people have inhaled Penicillium and possibly have become sensitized. There is no relation between Trichophyton tests and penicillin tests, however.

4. Fixed eruptions: These can be produced by streptomycin, chlortetracycline and oxytetracycline as well as penicillin. There exists a crossed sensitivity relationship between the latter two drugs, probably on an allergic basis (Aureomycin® and Terramycin®).

5. Early evanescent eruptions after large initial doses of antibiotics are seen. This is a function of the dosage, lasts only a few days, and subsides spontaneously. The onset is within twenty-four hours and retreatment is usually possible without untoward event. This is usually seen in patients with chronic infection, for example, furunculosis; hence, the mechanism here may be that of the Jarisch-Herxheimer type. It has been claimed that this group has become sensitized and then desensitized. However, they probably were never sensitive, as the truly allergic individual is desensitized only with great difficulty.

6. Eruptions in and about the mouth: These are erythematous and vesiculo-

papular eruptions of the buccal and pharyngeal membrane. The onset is usually forty-eight to seventy-two hours after therapy and follows most wide spectrum antibiotics and orally administered penicillin. There is probably an ecologic imbalance which accounts for this type of mechanism. Black, hairy tongue is rare.

7. Eruptions of the anogenital and other intertriginous areas: Slight erythema is seen, with severe, burning pain. Some are eczematous and one also can see a type which shows fine, shiny, red plaques associated with weeping. Diarrhea is seen associated with recovery of Monilia in the stools. The mechanism of these eruptions is not clear although such problems of vitamin deficiency, overgrowth of Monilia, or direct contact dermatitis from the antibiotic in the stool are considered.

Pellagrous dermatitis following the use of antibiotics is reported by Morris.[96] Thirty cases of this disorder are reported following the routine use of various antibiotics. It is believed that nicotinic acid metabolism is deranged by these agents. These patients are treated with niacin. Any patient who is taking an antibiotic and develops a pellagrous eruption, scrotal or rectal itching, or a photosensitivity reaction should be treated by this plan. The administration of nicotinic acid by mouth (100 mg three times a day) and cold saline compresses applied to the affected areas resulted in complete healing within twelve days.

The *Lancet*[33] commented editorially on this problem and warned against the indiscriminate use of penicillin. A report of the Ministry of Health in England shows that from a limited survey, 4.3 per cent of nurses working under local health authorities and 1.8 per cent of nurses working in hospitals have become sensitized to one or more antibiotics. Most of the sensitivities noted were skin changes.

An editorial[32] in the ANNALS OF ALLERGY quotes a survey by H. Welch and co-workers of institutions having 51,000 beds in a number of metropolitan hospitals. This is approximately 6 per cent of the total bed capacity of general hospitals in this country. In this group there were sixty-three patients who showed severe anaphylactoid shock, including nineteen fatalities from antibiotics. There were four reactions to streptomycin and the remainder were due to penicillin. Of twenty-five anaphylactoid reactions with five deaths reported to penethamate (Neo-penil®), the question of toxicity or allergy is raised. Among eighty-eight patients with reactions of some type to the antibiotics, twelve had previous evidence of sensitivity and twenty-six had a history of asthma.

Fatal and near fatal accidents with penicillin are also reported by Siegal[155] and others as well as by Feinberg and others[37] who repeatedly stressed the importance of care in the use of antibiotics. Stroud[165] reported the case of a physician, forty-seven years of age, who became weak, pale and cyanotic within a minute after a nurse injected 300,000 units of L-ephenamine penicillin in aqueous suspension gluteally because of asthmatic bronchitis. He became comatose in spite of epinephrine and cortisone administered intramuscularly. Other supportive therapy was used and the patient made a slow recovery. The fact that he recovered at all was due, the author believes, to the response to epinephrine which was given every seven to ten minutes in the first half hour in 0.5 cc doses. The total dosage of epinephrine given in the first twenty-four hours was 5.5 cc.

Sterling[161] is doubtful whether anaphylactic shock to penicillin occurs at the first injection. Considering the amount of penicillin used in medicine today, anaphylactic shock reactions are extremely uncommon, according to this author. He considered the five cardinal symptoms of impending

anaphylaxis to be syncope, burning or heat throughout the body, local or generalized pruritus, choking sensation in the throat, and severe paroxysmal pain varying in location but most usually in the chest.

Mayer[83] and others advise skin testing with a high dilution of penicillin before the administration of the drug to those patients presenting a positive or questionable history of sensitivity. They believed that the positive immediate skin test to this preparation contraindicates the further use of the drug, or it must be given as a calculated risk warranted by the seriousness of the illness and the specificity of the organism's reaction to penicillin.

Lowell[80] thought that the skin test as a means of determining sensitivity to drugs is of no appreciable value. He referred, however, to other than the antibodies. He has divided general drug reactions into four categories: (1) reactions characterized by generalized urticaria, edema, rhinitis and circulatory collapse; (2) reactions of erythema, eruption with or without pruritus, and fever; (3) symptoms caused by topical application of a drug which results in contact eczematous eruptions, and (4) reactions which are of such potential danger to the patient that further administration of the causative drug is clearly contraindicated. These reactions include the anemias, severe leukopenia, agranulocytosis, exfoliative dermatitis, nephritis and reactions associated with diffuse changes in blood vessels and connective tissue.

An anaphylactic reaction resulting from the topical application of penicillin to the mucous membrane is described by Weiss.[183] He reported a thirty-year-old woman who had received penicillin on many occasions and in the last illness she had received oral penicillin. She had mild tingling of the palms and soles and in the inguinal area. On the occasion of this communication she was given penicillin topically into an antrum and within a few minutes an acute anaphylactoid reaction occurred. She had no background of allergy. The author reported two similar cases from the literature.

Although the severity of the reactions to penicillin is alarming, the actual number is decreasing, according to Kitchin, Rein and others.[66] Reactions gradually decreased from 3.31 per cent in 1947 to 0.84 per cent in 1950. This could be attributed to the decreased use of penicillin in oil and wax and wide scale adoption of procaine penicillin which most workers agree is a much less reactive penicillin salt.

Sensitivity reactions to penicillin in children were studied by Collins and Vincent.[24] These authors agree with most pediatricians that reactions to penicillin are rare in children. They reviewed the records of the Hospital for Sick Children in Toronto, and were able to find only three cases of known sensitivity to this drug. In children with allergic backgrounds, however, penicillin reactions are not rare, as evidenced by a finding of 6 per cent reactions in this group of patients. Reactions noted have been skin eruptions. A careful history of exposure to the drug is mandatory. The authors believe that skin tests are not reliable.

Nelson and Braslow[104] reported the case of a girl, five and one-half months old, who received immune measles globulin, penicillin and chloromycetin for an attack of rubeola. A week later she was given a penicillin injection for diaper rash, accompanied by a fever of 102.2° F. Bullous-hemorrhagic gangrenous lesions of the buttock developed. The temperature rose to 105.6° F. Streptomycin, Aureomycin® and Terramycin® improved the eruption but the baby died. On the basis of the clinical pic-

ture, capillary plugs of the lungs found at necropsy, leukopenia and neutropenia, a diagnosis of fatal Shwartzman reaction was made.

In a panel discussion[12] on allergic reactions to penicillin with editorial comment by Schiller, several important points were made. Sherman, in this panel discussion, emphasized that a negative reaction to the scratch test or intracutaneous test is never a reliable index that the patient is not sensitive to penicillin. Patients with negative tests to penicillin have been known to have not only immediate reactions but in some cases delayed reactions to this antibiotic. Rose[12] again emphasized that penicillin should be used carefully and wisely since it is one of the most useful antibiotics at our disposal. An important comment is the fact that for immediate therapy of the near fatal shock reaction, he advised the intravenous administration of hydrocortone. This compound, 100 mg in 100 ml of 5 per cent dextrose, acts quickly and, according to Rose, is the most rapidly acting of all hormone preparations. At the moment, it is commercially available, and it would seem that all allergists would ultimately have this preparation available for allergic emergencies.

The life-saving properties of the corticotropins may be illustrated by the following brief report. The reviewer had occasion to see a woman, aged sixty-eight, who was a severe thyrocardiac; she was being hospitalized to control her hyperthyroidism before operation. She had been given digitalis, and was a poor operative risk. An intercurrent infection was treated with a single injection of penicillin and within twenty-four hours a generalized urticaria and localized angioneurotic edema had developed. The urticaria progressed on the extremities to lesions of erythema multiforme with bullae, petechiae and ecchymoses. The general condition of the patient deteriorated rapidly and the internists who saw her despaired of her life. In this desperate situation the reviewer suggested the intravenous administration of 100 mg of ACTH in 500 cc of 5 per cent glucose. The infusion was given over a ten- to twelve-hour period and was repeated until the patient rallied from her moribund condition. The dosage was then gradually reduced and all evidence of her skin hypersensitivity disappeared over the ensuing seven to ten days. Although cardiac failure is usually a direct contraindication to the administration of ACTH, this patient not only tolerated a tremendous dose of corticotropin but also improved sufficiently so that cardiac embarrassment was never a complicating feature of her hospitalization.

Rostenberg[129] has investigated some of the mechanisms by which drugs and antibiotics produce their reactions, and summarized his opinions under the following headings:

1. Enzyme interference. This may be cellular competition or actually poisoning of the enzyme system. Examples of this are the light sensitivities seen from sulfones and the keratoses after long-continued Fowler's solution (arsenic).

2. Intolerance or idiosyncrasy. Intolerance suggests a quantitative deviation in response. Quinine produces tinnitus and this is probably a form of intolerance. Idiosyncrasy is considered to be a more fundamental and inborn trait which produces a qualitative deviation in response. The distinction between intolerance and idiosyncrasy cannot be too finite. There is probably considerable overlapping.

3. Allergy. One can see an immediate response to an allergic drug such as penicillin, in which case urticaria or serum sickness develops. The periarteritis of sulfone sensitivity is a more subacute or chronic form of allergic response. A delayed type of allergy is exemplified by the eczematous response and exfoliative dermatitis seen with arsenicals.

4. Herxheimer reaction. In considering the Herxheimer reaction, one must remember that the specific drug kills a specific organism. Since there are many other organisms concerned at the time, the destruction of the specific organism or other organisms, or both, may produce products which in themselves cause symptoms because of allergy of the host to these breakdown products. A certain type of eruption known as penicillids is manifested by dyshidrotic lesions. This is probably not an allergic response because many patients again tolerate penicillin without the production of these specific skin changes.

5. Ecologic mechanisms. By this is meant that there is a certain organism-to-organism and host-to-organism relationship which may be disturbed under certain situations. There appears to be a disturbance of the organism-to-organism relationship in the giving of broad spectrum antibiotics, which is followed by an overgrowth of Monilia, for example.

6. Biotropism effect. Drugs produce a necrotropic effect on organisms by mechanisms, mostly unknown, by which they destroy such organisms. There is, however, a further action or biotropic effect in which one assumes that a certain drug which may kill certain organisms is stimulating to other organisms. For example, in Milian's ninth-day erythema, one could suppose that the drug enhances the scarlatiniform organisms to produce this type of erythema. There is further evidence to show that sulfones may be responsible for the production of erythema nodosum by this biotropic mechanism.

Crissey and Coccamise[27] have observed skin reactions with the use of five of the most widely employed antibiotic preparations. Dermatologic manifestations of penicillin sensitivity are described and these include urticaria, angioedema and serum sickness. Other dermatologic evidence of penicillin sensitivity can be described as vesicular phytid reactions and exfoliative dermatitis. Serum sickness type of penicillin sensitivity occurred in 6 per cent of the patients observed by these authors. Oral penicillin has a very low incidence of sensitivity. Following the use of streptomycin, the authors observed the presence of maculopapular eruptions, toxic erythemas, urticaria and exfoliative dermatitis. A more extensive involvement was manifested by purpura, erythema nodosum and erythema multiforme. Aureomycin® may be responsible for fixed drug eruptions, urticaria, photosensitization phenomena and anogenital dermatitis.

The general field of drug allergy has been expertly reviewed by Brown.[14] For convenience in study, the drugs are arranged in order most likely to cause allergic reactions. The most important drugs, together with their commonest allergic reaction, are listed and arranged for easy reference to the practicing allergist. A phenobarbital sensitivity syndrome is described by McGeachy and Bloomer.[84] Fever, mental confusion and toxic damage to the structure of essential organs were accompanied by an erythematous eruption in one female and two male patients. Two of the three patients so recorded died. There was widespread cellular damage of important viscera. It is noteworthy that intravenous procaine helped one of the patients. Theodore[174] makes a comparison between true drug sensitivity and drug irritation in the conjunctiva. Itching dermatitis, catarrhal conjunctivitis and conjunctival eosinophilia or basophilia are the characteristics of drug sensitivity of the contact type in and around the eye. Drug irritants, on the other hand, cause their reaction by direct conjunctival primary irritation. The alkaloids, especially the myotics and related compounds, are likely to be included in the primary irritant group. Berkowitz, Glaser and Johnstone[10] were interested in the incidence of allergy to drugs in pediatric practice. In an over-all study comprising reactions to many drugs it could be determined that there was a higher incidence of reaction in allergic children. Reactions were noted in 20 per cent of allergic children compared to 2.4 per cent in nonallergic children.

Morris and Cohen[100] studied cross sensitivity between diphenylhydantoin sodium and phenobarbital. They described a patient who developed dermatitis medicamentosa due to phenobarbital after taking the drug for two years. The eruption cleared after discontinuing the drug, and diphenylhydantoin sodium was given. Within forty-eight hours the skin eruption reappeared. Another patient is described who had the reverse type of cross sensitization. Similarity in the chemical structure of these compounds accounts for the appearance of cross sensitivity. A further report on epidermal sensitization due to sulfonamide drugs is presented by Kooij and van Vloten.[70] The authors studied fifty-four patients with sulfonamide dermatitis. Group and cross-sensitizations could be demonstarted in most patients by patch tests. Chemical compounds containing $NH_2C_6H_4$ configuration in common with the sulfonamides were found to cause positive reactions in patients sensitized to the sulfonamides. This compound is contained in aniline dyes, hair dyes, local anesthetics, procaine penicillin, para-aminobenzoic acid, neoarsphenamine, and para-aminosalicylic acid. The authors believe that hypersenstivity to sulfonamides persists throughout life. Attempts at antibody discovery with Prausnitz-Küstner and Urbach-Koenigstein methods were negative. The Leftwich reaction was unreliable and intracutaneous tests with sulfanilamide azoproteins gave negative results, as did patch tests with the same material. This again points to the inevitably poor results obtained with skin testing in determining drug sensitivty.

Hypersensitivity to procaine amide hydrochloride is reported by Koffler[69] who recorded a cardiac patient to whom 50 mg of procaine amide hydrochloride was administered orally. Within twenty minutes the pulse became regular and remained so for about two hours, after which time cardiac irregularity recurred, but less frequently. Previous work with this preparation had demonstrated its use in the suppression of premature ventricular contractions. In this patient, however, symptoms of generalized reaction characterized by marked pruritus and edema appeared about twenty minutes after ingestion of the drug. The allergic symptoms improved in about one hour with the use of antihistaminics. That anaphylactic death can result from the administration of procaine hydrochloride is the basis of the report by Criep and Ribeiro.[26] These authors believe that it is necessary to publicize the fact that severe or even fatal reactions may occur from a drug that is thought to be comparatively safe. Reactions to local anesthetic drugs such as procaine may be divided into those which occur on a toxic basis and those which are characterized by hypersensitivity. It must be remembered that skin tests are of no diagnostic value in determining sensitivity to a drug such as procaine, since this material is not of a protein nature.

The authors recommend that before procaine, cocaine and related drugs are used, they should first be applied intranasally with an applicator. If sensitivity is present to a marked degree, untoward symptoms will develop within a few minutes. If there is a negative response to this means of testing, the authors believe that the administration of the drug should be comparatively safe. Angerer, Su and Head[3] reported a death following the use of efocaine. This is a long-lasting or slowly absorbable procaine preparation. The patient was given an intercostal injection of this preparation. Other complications from this preparation have been transverse myelitis, toxic neuritis and sloughing of perirectal tissues. The agent has been extensively used for the symptomatic treatment of pruritus ani.

An allergic reaction to heparin is reported by Midttun.[86] The patient

under study went into a state of collapse, lasting for five minutes, immediately after the injection of heparin. Positive reactions were obtained to intracutaneous and passive transfer tests with heparin. A second patient suffering from myocardial infarction developed a prickling sensation of the skin, generalized erythroderma, dizziness and vomiting within five minutes after the injection of heparin. This patient also showed positive intracutaneous and passive transfer reactions to heparin.

Excess of vitamin A may cause symptoms which resemble hypersensitivity. Harrison and Mercer[54] reported a twenty-eight-month-old child who developed hyperirritability, cheilosis, pruritus and swellings resembling angioedema along the ulna bones and along the fifth metatarsals. The symptoms subsided when the vitamin was discontinued.

Dalgleish[29] reported a fulminating polyarthritis which occurred after repeated courses of thiouracil and antithyroid drugs. The patient was being treated for hyperthyroidism and an eruption, ankle edema and thrombophlebitis of the legs developed. Following withdrawal of the thiouracil her symptoms cleared rapidly. Ten days later thiouracil was repeated and weakness, malaise, pain and fever immediately developed. Within two weeks following the beginning of her second course of thiouracil the patient died. Postmortem examination showed diffuse vascular disease throughout the body.

A clinical picture resembling infectious mononucleosis following the use of para-amino-salicylic acid is described by Sjoukes[156] and others. Five patients were observed in whom a clinical syndrome resembling infectious mononucleosis developed following the administration of this drug. Symptoms included headaches, fever, general malaise, exanthem, swelling of the lymph nodes and a blood picture consisting of lymphocytosis with pathologic mononuclear cells. Three patients had splenomegaly. Symptoms cleared when the medication was discontinued and recurred when treatment was resumed. Shatin, Canizares and Worthington[148] reported a lichen planus-like drug eruption following the use of para-amino-salicylic acid. The usual type of eruption seen after administration of this drug has been either morbilliform or scarlatiniform. Five cases, however, were reported by these authors which presented an eruption resembling lichen planus. In two of these patients there were erosive mouth lesions involving tongue and buccal mucosa. Phenylbutazone, a drug which has recently been introduced, has had a widespread use in internal medicine. Charet and Siegel[20] as well as Nathan and others[103] have reported unusual reactions from this drug. There is a definite relationship between the chemical formulas of aminopyrine and phenylbutazone. Many toxic manifestations have appeared from the use of this drug in the treatment of arthritis and allied rheumatic disorders. A fatality is reported which was thought to be due to overwhelming toxicity and possible hypersensitivity to this drug. Allergic manifestations were related primarily to the reactions in the skin and viscera. In spite of the prompt cessation of the drug and use of counter measures, the reported patient's clinical status continued to deteriorate, with ultimate death. Focal areas of infiltration of lymphoid cells in the adrenal cortex and medulla with degeneration of cortical cells were seen at autopsy. ACTH was used for this patient, but to no avail.

Clark and McNaughton[21] reported exfoliative dermatitis due to Banthine® in a sixty-year-old white man who developed an acute exfoliative dermatitis on the eighth day of treatment with this preparation. It is used extensively in the treatment of gastrointestinal complaints, es-

pecially peptic ulcer. After the skin cleared, patch tests performed with crushed Banthine tablets elicited positive reactions. Control tests made on normal subjects and other patients taking Banthine gave negative reactions.

A fatal case of mercurial dermatitis with peculiar visceral involvement is reported by Brück and Norman.[15] The patient, a man aged twenty-three, had a severe, extensive dermatitis from the local application of a mercurial powder. A week or two after the eruption subsided, attacks of wheeze, cough and dyspnea developed. Roentgenograms of the chest showed extensive, coalescent, massive, parenchymal shadows, mottled in appearance and involving both lungs. A question of sarcoidosis arose. Three months later the films showed some regression of the infiltration. Two years later dermatitis again developed from the use of mercurial ointment, and this time he was treated with penicillin. On the second hospital day his condition became critical. Cyanosis, dyspnea and tachycardia and signs of cerebral involvement developed and he died twenty-four hours later. There seems to be a connection in this patient between the mercurial dermatitis and a pulmonary lesion involving edema, possibly interstitial hemorrhage similar to Löffler's syndrome, which ultimately led to fatal pulmonary and right ventricular circulatory failure.

Similar to digitalis, allergy to quinidine is not common. Three cases were observed in which fever ranging up to 104 degrees F. occurred following quinidine administration. Rose, Vogl and Turtz[126] reported that in each patient the fever was associated with a macular eruption which was often pruritic. The reactions occurred shortly after the administration of the second course of quinidine in two patients and in the third patient, after the drug had been administered for two weeks. The authors reported a positive skin reaction in one patient, obtained with an intradermal test with quinidine hydrochloride, and a similar control test performed on a normal subject was reported negative.

Although urticaria and angioedema, as well as serum sickness, are troublesome enough as complications of drug eruption, the serious problems are the patients who present hypersensitivity demonstrated by allergic purpura or the various anemias and bone marrow depressions. Ackroyd[1] described allergic purpura, including purpura due to foods, drugs and infections. Allergic purpura is divided into two types. The first is the type that is associated with an erythematous exanthem and also with joint and visceral symptoms, the Henoch-Schönlein syndrome. The second is the true purpura which is not associated, as a rule, with an erythematous exanthem. Henoch-Schönlein disease, although regarded generally as an allergic disturbance, is due to food sensitivity in only a small percentage of patients.

In most cases, the etiologic factor cannot be established. A careful food history, trial diets and elimination diets may be of assistance in identifying an offending food. Skin tests are seldom helpful. The second type occurs in the absence of any inflammatory or exanthematous reaction and is referred to here as true purpura. It may be due to an abnormal response to an infection or to a drug, but is rarely if ever caused by food. Purpura due to drugs has been reported following the use of a large number of agents. A drug may have been taken over a period of a few days, weeks or even years without untoward results. Finally, after a single dose, purpura may suddenly appear. Persistent use of a drug in the presence of hypersensitivity may result in a fatal reaction. Sensitivity to any drug

may persist for years after administration of the drug has been discontinued.

Osgood[112] classified drugs producing bone marrow depression in susceptible individuals. The commonest drugs known to produce this effect include the anticonvulsants (Mesantoin®), antihistaminics, antimicrobial agents (arsenicals and Chloromycetin®), antithyroid agents (thiouracil), sedatives (Sedormid® and aminopyrine), spasmolytics (phenothiazines), gold preparations, phenolbutazone and nitrophenols. In studying the progress of a patient with agranulocytosis, it is important to have serial determinations of the hemoglobin concentration, leukocyte count, reticulocyte count, and clot retraction time. The treatment includes daily penicillin and streptomycin intramuscularly, fresh whole blood not over six hours old, every six hours if necessary. Cortisone and ACTH are also indicated.

Heck[56] also reported on the influence of drugs on blood and bone marrow and made the point that hematologic reactions may be evidenced by a change in a single element of the blood, in all elements, or in various cellular combinations. The end result of the sudden or gradual response may be reversible or irreversible upon withdrawal of the offending drug. Granulocytopenia may be initiated with an acute onset and the patient may have chills, sore throat, generalized aching and fever. There is a leukopenia, with a decrease or disappearance of neutrophilic elements. The author mentioned the same group of drugs previously quoted by Osgood.

Scalettar and Mazursky[136] reported secondary thrombocytopenic purpura following DDT exposure. The case of an eleven-month infant is recorded who was admitted to the hospital with epistaxis, petechiae and ecchymoses. The only positive history was that the patient's home had been sprayed daily with a 5 per cent DDT mixture, and a powder containing DDT had been placed along the walls. The infant had been crawling and playing on the floor. The bone marrow showed adequate megakaryocytes but no platelets. Within a few days, without any specific therapy, the lesions began to fade. No repeat tests were made with DDT.

Kresbach[71] likewise reported DDT dermatitis with systemic involvement. A patient aged fifty-three used a fly spray containing 10 per cent DDT solution. A few days later the patient noted intense redness and swelling on the exposed parts, particularly on the face and flexor surfaces of the forearms, together with severe itching and recurrence of the dermatitis of the legs. Patch tests were positive with 10 per cent DDT solution, 1 to 100 and 1 to 500, applied to the normal skin. Subsequent exposures to DDT led to hospitalization of the patient, who was jaundiced and showed liver enlargement. Therapeutic improvement was noted with the administration of BAL. In these drug hypersensitivities the patient usually improves when the offending agent is recognized and eliminated. This is an ideal situation in which the corticotropins are helpful. Baylor and Toone[8] reported the successful treatment of a number of cases of gold dermatitis with corticotropins.

ALLERGY OF INFECTION

There are a number of studies which indicate that patients with Hodgkin's disease and other lymphomas present, in some stage of the disease, an anergic reaction to tuberculin and Trichophyton. In the few patients with mycosis fungoides studied by the reviewer, some patients were hyperergic to these antigens and a negative reaction has not as yet been seen in these patients. Rostenberg[131] studied the blocking effect of plasma

and lysed red blood cells on delayed reactions. He took various dilutions of old tuberculin and Trichophyton with donors' plasma or lysed red blood cells from patients with sarcoidosis, Hodgkin's disease, papulonecrotic tuberculid and nonsarcoid patients. A material (anticutin) capable of blocking the delayed type of allergic response can be found in human blood. Better reactions are obtained from lysed red blood cells. The blocking effect with the same serum varied from recipient to recipient. The same blood may block either Trichophyton, or tuberculin or the tuberculin reaction, or both.

Nummular eczema is a term applied to an eczematous eruption appearing in circular plaques, usually on the extremities, which often present the appearance of a group of studded vesicles or simple erythema and scaling. The etiology has been obscure. Fowle and Rice[43] considered the possibility that nummular eczema is a manifestation of bacterial allergy. The authors studied 178 cases of nummular eczema and 422 cases of other eruptions of the hands. They thought that nummular eczema can be satisfactorily explained by the triad of etiologic components: poor nutrition, bacterial allergy to staphylococci, and bacterial invasion of the skin by staphylococci. Analysis of the records indicated that patients ate small quantities of concentrated carbohydrates and fats. There were focal flare-ups of nummular eczema after overdosing with staphylococcus vaccine-toxoid. Generalized vesicular eruptions occasionally occur after an accidental intravenous injection. Exact statistical data of the appearance of staphylococci flora in nummular eczema as compared to eczematous eruptions are not given. Autosensitization dermatitis was first described by Whitfield. Lipschultz[76] believes that the antigen responsible for cutaneous autosensitization is probably bacterial in origin not limited to any bacterial species but usually made up of the ordinary constituents of normal skin flora. Incubation of these bacteria was carried out with substances derived from epidermal cells and keratin. Leukocytes seem to be antigen transporters from the site of formation to the reticulo-endothelial system.

Occurrence and typing of Staphylococcus pyogenes in weeping eczema and the role played by these bacteria in the pathogenesis and course of eczema are described by Andersen and Heilesen.[2] These authors made bacterial patch tests using bacteriophage-typed and serologically-typed Staphylococcus pyogenes strains. Three antigens were distinguished: (1) heat stable and resistant to autoclaving; (2) heat labile and (3) trypsin labile, heat labile. Seventy patients with various forms of eczematous dermatitis were studied. Patch tests caused positive reactions with Staphylococcus pyogenes in about 68 per cent; 47 per cent of these patients were treated effectively with penicillin. It is accepted by many dermatologists that pyogenic and other microorganisms play a role in many cases of eczematous dermatitis. This role is probably secondary and studies of this type will enable us to understand the over-all problem in eczema.

MISCELLANEOUS ALLERGIES

Solar reactions may be classified in four categories. Kesten and Slatkin[63] placed solar erythema, urticaria and photodynamic dermatitis in the first category. Porphyria, hydroa vacciniforme and epidermolysis bullosa make up the second category. The third classification includes pellagra, lupus erythematosus, papular urticaria and others. Chronic sunburn, epithelioma and degenerative diseases of collagen and elastic tissue are included in the fourth category. Various protective agents against the sun are discussed by these authors, using chemical agents in various oint-

ment bases. A more recent treatment for light sensitivity using Atabrine® or Chloroquine is described by Knox, Lamb, Shelmire and Morgan.[68] Eighteen individuals with light sensitive eruptions showed improvement following systemic administration of either of these agents. No explanation seems to be readily available to account for the beneficial effect of these drugs on patients with actinic dermatitis. As is well known, discoid lupus erythematosus also is improved by these agents. The drug is excreted in the sweat and is known to interfere, in some cases, with normal sweating. In hot climates, therefore, where light eruptions are more frequent, patients must be observed carefully for evidence of acute sweat retention. An unusual form of solar dermatitis is reported by Morgan and Shackleford.[89] These authors reported three patients who developed extreme forms of light sensitiveness manifested by vesiculobullous and prurigo-like lesions with scarring of the exposed areas. Complete studies revealed liver damage or disease in all three patients. Antigen was likewise found which affects the production of melanin. Because of the lack of black melanin in the basal cells of the epidermis, strong sunlight is not filtered from the corium with subsequent damage to the dermal vessels and collagen.

Many hand eruptions are seen by dermatologists and allergists which show nothing but a mild erythema and vesiculation. The vesicles occur usually in crops along the sides of the fingers and they do not seem to be an "id" response. The name pompholyx has been assigned to this condition. Wilson and Thackray[184] as well as Devine[30] have studied the pompholyx vesicles in their relation to sweat ducts. The authors reported that many vesicles seen in this condition show the sides of the vesicles to be intact. No abnormal fluid space is noted between the cells to suggest sweat extravasation. No distention of sweat ducts was observed. In some instances ducts actually passed through vesicular cavities without becoming involved in the vesicular process.

Ferris, Alpert and Coakley[38] reported on the use of an antihistaminic in the prevention of allergic transfusion reactions. Pyribenzamine,® 1 cc containing 25 mgs, was added to the blood to be transfused in a series of 607 blood transfusions. In this group there was one allergic reaction, no pyrogenic reactions and one hemolytic reaction, and in a controlled group of 724 transfusions in which no antihistaminic was used, twenty-one allergic reactions were noted. Although these authors reported a series with Pyribenzamine, the same effect can be obtained with most of the injectable antihistaminics.

A review of the recent studies in heat and cold hypersensitivity is presented by Kierland.[64] No established treatment except antihistaminics, nicotinic acid and graduated exposure to other physical agent is presented.

An unusual finding is reported by King and Forrest[65] in a six-year-old female child who, following vaccination on the arm, developed vaccinia of the eyelids. The diagnosis was proved by animal inoculation and cultures. The response to Aureomycin® was dramatic. Although the reported case was not an allergic patient, the disease is most commonly seen in eczematous infants and therefore knowledge of its treatment is essential to the pediatric allergist.

Rockwell and Johnson[124] reported on insect bite reactions. Asthma, generalized urticaria and anaphylactic reactions from bee and wasp stings have been reported by a number of observers. These authors differentiated three types of allergic reaction to mosquito bites: an urticarial response, a tuberculin type or eczematoid reaction may be seen. These reactions may

be duplicated with patch and intradermal tests, using crude aqueous mosquito extracts. A high percentage of persons with severe mosquito bite reactions give a personal or family or both, history of other hypersensitivity reactions. Usually multiple allergens are involved. Extracts of various isolated portions of the mosquito produce similar reactions on sensitive individuals. Antihistaminics and alkalinizaton did not significantly alter the bite reaction. O'Rourke and Murnaghan[111] could favorably influence the reaction to the bite of the mosquito by the use of a 2 per cent Pyribenzamine cream. This was applied immediately after the bite was received. The application relieved the pruritus and was also effective in reducing the severity of the subsequent lesion. The reactions of thirty-six medical students to the bites of the mosquito *Aëdes aegypti* were recorded. One per cent nupercaine ointment, locally applied, produced comparable results. A review of the literature of hypersensitivity to bee stings as well as the report of a fatal case was made by Schenkin[138] and others. They collected ten reported fatal allergic reactions. Their own patient, when he was eighteen years of age, developed abdominal cramps, diarrhea and vomiting following a bee sting. The same situation developed at the age of twenty. At twenty-one, a bee sting in the temple area was followed by collapse and death within twenty-five minutes. Autopsy findings showed anaphylactic-like changes in the lungs. Mueller and Hill[102] have studied a number of children who present unusual reactions to bee and wasp stings. These patients have been treated with mixed bee and wasp antigens, with favorable clinical results. The reviewer notes that the histopathologic picture of an insect bite in the allergic individual may closely simulate a lymphomatous response in the tissues. Hence the pathologist must be informed of the clinical data before the final diagnosis is accepted in a patient in whom the diagnosis of lymphoma is considered.

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DECREASED SALT INTAKE AMONG NON-SMOKERS DOES NOT REDUCE HYPERTENSION

Individuals over forty who had decreased their salt intake for ten years and who do not smoke showed a higher prevalence of hypertension according to a preliminary inquiry among 799 persons, according to an article by Dr. C. A. D'Alonzo of the E. I. Du Pont de Nemours & Co., of Wilmington, Delaware, published in the November issue of *Industrial Medicine and Surgery*. The study also confirms previous indications that there is a greater chance of the children having hypertension when one or both parents have it than when neither parent has it. Dr. Alonzo says, "It is interesting that this chance seems to be slightly greater when the mother has hypertension than when the father has it."

News Items

ACADEMY OF PSYCHOSOMATIC MEDICINE

The Academy of Psychosomatic Medicine held its first annual meeting at the Plaza Hotel, New York City, on October 8-9, 1954. Over one hundred Fellows and guests attended the two-day session, devoted to "The Psychosomatic Aspects of Surgery."

The speakers included, among others, Drs. E. A. Rovenstine, Charles P. Bailey, William S. Kroger, Lester L. Coleman, T. F. Schlaegel, Jr., Arthur J. Barsky, C. D. Haagensen, and John A. P. Millet. A panel discussion on "What Every Physician Should Know About the Psychosomatic Aspects of Surgery" was moderated by Dr. Herbert Conway, the members of the panel being: John M. Cavanagh, Samuel P. Harbison, Albert S. Lyons, John A. P. Millet, Harold Rosen, and Somers Sturgis. Plans are being made to publish the papers in book form.

The Society voted to extend the present incumbents in office for an additional year: president, Dr. William Kaufman, Bridgeport, Connecticut; vice president, Dr. Bernard B. Raginsky, Montreal, Canada; secretary, Dr. Ethan Allan Brown, Boston, Massachusetts; treasurer, Dr. Alfred J. Cantor, Flushing, New York; and historian, Dr. Robert S. Drews, Detroit, Michigan.

The second annual meeting will be held again at the Hotel Plaza, October 6-8, 1955. The general subject decided upon is "The Psychosomatic Aspects of Drug Administration." Those who wish to present papers at this meeting are invited to communicate with the program chairman, Dr. Ethan Allan Brown, Boston, Massachusetts, from whom applications for Fellowship and a copy of the constitution may also be obtained.

The third annual meeting is planned for the Edgewater Beach Hotel in Chicago, in October, 1956. The program chairman will be Dr. William Kaufman, and the subject tentatively chosen is "The Psychosomatic Aspects of Endocrine Disorders."

CANADIAN ACADEMY OF ALLERGY

The Canadian Academy of Allergy will hold its annual meeting along with the Canadian Medical Association at its conjoint meeting with the British Medical Association and the Ontario Medical Association at the Royal York Hotel in Toronto, Ontario, on Tuesday, June 21, 1955. Dr. David A. Long of the National Research Council, Mill Hill, London, England, will be the chief guest speaker, and his topic will be "The Influence of Nutritional and Hormonal Factors Upon the Immune and Allergic Responses to Infection." Dr. Robert A. Cooke, Director of the Institute of Allergy, Roosevelt Hospital, New York, Dr. Bram Rose of Montreal, and Dr. C. H. A. Walton of Winnipeg will also take part in the program.

NOTICE

By order of the Board of Directors, all members more than six months in arrears in the payment of their College dues will no longer receive the Annals following this issue.

THE AMERICAN COLLEGE OF ALLERGISTS

Eleventh Annual Instructional Course and Congress

Morrison Hotel, Chicago, Illinois

April 25-30, 1955

The *Eleventh Annual Instructional Course,* April 25-27, 1955, with Dr. Orval Withers, Chairman, and Dr. Morris A. Kaplan, Co-Chairman, will be held at the Morrison Hotel in Chicago. A tentative program has now been set up, but this, of course, is subject to change. Watch future issues of the ANNALS OF ALLERGY for important announcements and complete program.

As the Instructional Course is set up at the present time, Monday morning, April 25, will be devoted to the subject of FUNDAMENTALS OF ALLERGY, with lectures on Classification of Hypersensitive States, Principles of Immunology, Pathology and Physiology of Allergy, Diagnosis in Allergy, et cetera. The first luncheon speaker will discuss "Immunologic Aspects of Blood Dyscrasias." The afternoon session will be devoted to RESPIRATORY ALLERGY and will be comprised of lectures on Nasal Allergy; Pharmacology of Antihistaminic Drugs; Classification and Diagnostic Procedures in Bronchial Asthma; and Differential Diagnosis from Cardiovascular and other Pulmonary Conditions. Evening panel discussions will be held on Indications and Techniques of Various Pulmonary Pressure Machines, Inhalant Therapy in the Treatment of Bronchial Asthma, and Emphysema and Other Chest Conditions.

On Tuesday morning, April 26, the subject of RESPIRATORY ALLERGY will be continued, with lectures on the Management of Acute Attacks, Chronic Attacks, Smoker's Asthma, Postural Drainage, and Chemotherapy. The luncheon speaker will present a talk on "Chronic Emphysema and Its Management," and the afternoon session will be devoted to DERMATOLOGIC ALLERGY with papers on Electrolytes in the Treatment of Infantile Eczema, Pitfalls in the Diagnosis of Infantile Eczema, Symptomatic Treatment of Infantile Eczema, Common Causes of Contact Dermatitis, Modern Therapy of Atopic and Contact Dermatitis in Adults, Drug Allergy, Common Causes and Management of Urticaria and Angioneurotic Edema, and Allergic Purpura. Tuesday evening will be given over to a panel discussion on Office Management.

Wednesday morning, April 27, the subject will be NEWER CONCEPTS OF ALLERGIC CONDITIONS. Papers will deal with Pulmonary Function Tests, Cor Pulmonale, Endocrines, Pharmacology of Allergic Disorders, Newer Aspects of Psychotherapy in Allergic Practice, Management of the Pre-Allergic Child, and Special Problems in the Treatment of Bacterial Allergy. Miscellaneous topics will be considered on Wednesday afternoon, after a nationally-known speaker has presented a paper at the noon luncheon. The afternoon subjects will cover Allergy of the Alimentary Tract, Psychodynamics in Childhood Allergy, Immunologic Aspects of Idiopathic Acquired Hemolytic Anemia, Headache, Insect Allergy, Physical Allergy, Industrial Allergy, and other topics. The Wednesday evening session will consist of two panels: Mold Allergy and Questions, Please.

The General Scientific Session starts on Thursday morning, April 28, and papers of fifteen or twenty minutes' length will be presented during the entire day. A banquet with special entertainment is scheduled for the evening.

Friday morning will be devoted to PEDIATRIC ALLERGY, followed by two round table luncheons: one on Pediatric Allergy and the other on Ophthalmic and Otorhinolaryngologic Allergy. At the afternoon session the President's address will be given followed by the guest speaker, Dr. Robert Cooke, of New York City. There will be two sessions on Friday evening, one on Dermatologic Allergy and the other a Psychosomatic Workshop.

The Committee on Ophthalmic and Otorhinolaryngologic Allergy will be in charge of the Saturday morning session.

Further details have already been sent you in a *News Letter,* together with a hotel reservation card. All reservations must be made direct to the Morrison Hotel on the form enclosed with the *News Letter.* The final program will appear in the January-February ANNALS.

MESSAGE TO THE WIVES OF OUR COLLEGE MEMBERS, SUSTAINING MEMBERS AND HONORARY MEMBERS

On April 8, 1954, the Women's Auxiliary of The American College of Allergists, Inc., was formed. Membership applications were sent to all of the wives, and the response has been wonderful. Charter Membership is limited to those joining within one year from date of organization, and to date we have 174 Charter Members.

We are inserting this note in the ANNALS, as a reminder that only a few months remain in which to become a Charter Member. If you have overlooked or misplaced your application, you may use the one on this page.

The initial fee for becoming a member is five dollars ($5.00), and the annual dues is five dollars ($5.00), both payable in advance. Complete the application, detach, enclose your check for ten dollars ($10.00) made payable to Women's Auxiliary, American College of Allergists, Inc., Eunice Swinny, Treasurer, and send to Mrs. Boen Swinny, 143 Bluebonnet Blvd., San Antonio 9, Texas.

MRS. J. WARRICK THOMAS
Secretary

MRS. MORRIS A. KAPLAN
President

Application for Membership

DATE.....

NAME .....

MAIDEN NAME .....

HOME ADDRESS .....

CITY ..... ZONE .... STATE .....

GRADUATE SYMPOSIUM ON GERIATRIC MEDICINE

A Graduate Symposium on Geriatric Medicine was presented by the American Geriatrics Society on November 12 and 13, 1954, at Hotel Roosevelt, New York City. Dr. Edward Henderson, Editor-in-Chief of *The Journal of the American Geriatrics Society*, arranged the meeting.

The following program was presented: "Geriatrics—A Definition," Dr. Marvin Weinberg, New York; "Low Dosage Androgen-Estrogen Therapy in the Male and Female Older Age Group," Drs. Charles H. Birnberg and Raphael Kurzrok, Jewish Hospital, Brooklyn, New York; "Male Climacterium," Dr. Thomas H. McGavack, New York Medical College, New York; "Recent Progress in Cancer Research," Dr. Cornelius P. Rhoads, Sloan-Kettering Institute for Cancer Research, New York; "Project and Technique Rationale of Sex Steroid Replacement in the Neutral Gender," Dr. William H. Masters, Washington University, St. Louis, Missouri; "Prostatic Obstruction in the Aged," Dr. Robert S. Hotchkiss, Bellevue Medical Center, New York; "Surgical Alleviation of Parkinsonism: Effects of Occlusion of the Anterior Choroidal Artery," Dr. Irving S. Cooper, Bellevue Medical Center, New York; "The Endocrine Glands and Their Ability to Stabilize the Body Function under Stress Conditions," Dr. William B. Kountz, Washington University, St. Louis, Missouri; "Emergency and Prophylactic Corticoid Therapy in Individuals Past Fifty," Dr. Laurence W. Kinsell, Institute for Metabolic Research, Oakland, California; "Nutrition and Aging," Dr. Fredrick J. Stare, Harvard University School of Public Health, Boston, Massachusetts; "Recent Advances in the Treatment of Senile Vaginitis, Kraurosis, and Leukoplakia," Dr. Charles Lee Buxton, Yale University School of Medicine, New Haven, Connecticut; "Obesity and Diabetes: Two Related Problems of Later Life," Dr. C. N. H. Long, Yale University School of Medicine, New Haven, Connecticut; "The Preparation of the Geriatric Patient for Surgery on the Biliary Tract," Drs. Frank Glenn and Richard Karl, Cornell University Medical College, New York; "Respiratory Allergy and its Modifications in Patients Over Forty-five Years of Age," Dr. Fred W. Wittich, American College of Allergists, Minneapolis, Minnesota; "Ovarian Function in Menopausal and Post-menopausal Women," Drs. C. Alvin Paulsen, William O. Maddock, and Robert B. Leach, Wayne University College of Medicine, Detroit, Michigan.

"Gynecologic Cancer in the Older Patient," Dr. John McLean Morris, Yale University School of Medicine, New Haven Connecticut; "Clinical Studies in Prostatic Cancer," Dr. William Wallace Scott, Johns Hopkins University School of Medicine, Baltimore, Maryland; "Cortisone in the Treatment of Advanced Cancer," Dr. Carlos P. Lamar, University of Miami Medical School, Miami, Florida; "The Influence of Emotional Attitudes on the Aging Process," Dr. David C. Wilson, University of Virginia School of Medicine, Charlottesville, Virginia; "Problems of Chemotherapy in the Older Age Groups," Dr. David Lehr, New York Medical College, New York City; "Elevated Titers of Steroids in Obese Men and the Possibility that Steroids Promote Some of the Adverse Effects Associated with Obesity," Dr. James B. Hamilton, State University of New York College of Medicine, Brooklyn, N. Y.; "The Advantages of the Use of Unrestricted Diet in the Treatment of Peptic Ulcer in the Aged," Dr. Edward A. Marshall, Huron Road Hospital, East Cleveland, Ohio; "The Pros and Cons of Estrogen Administration after the Menopause," Dr. E. Kost Shelton, University of California at Los Angeles, California.

"Cortisone in the Immediate Therapy of Apoplectic Stroke," Dr. Henry I. Russek, Staten Island Hospital, Staten Island, New York; "The Relationship of Blood Lipids to Coronary Heart Disease," Dr. Menard M. Gertler, Bellevue-Medical Center, New

York City; "The Effects of Sitosterol and Lipotropes on the Blood Lipids and the Clinical Course of Angina Pectoris," Dr. Charles F. Wilkinson, New York University Medical School, New York City; "Recent Developments in the Treatment of Hypertension," Dr. Edward D. Freis, Georgetown University School of Medicine, Washington, D. C.; "Heart Disease and Obesity," Drs. Arthur M. Master and Harry L. Jaffe, Columbia University College of Physicians and Surgeons, New York City; and a "Panel Discussion on Heart Disease" by Drs. Freis, Gertler, Lehr, Master, Russek, and Wilkinson.

The symposium was made possible by a grant from the Schering Corporation, Bloomfield, New Jersey.

PENNSYLVANIA ALLERGY ASSOCIATION

The Pennsylvania Allergy Association held its Fall Session on Thursday, November 4, 1954, at the Penn-Alto Hotel, Altoona, Pennsylvania. Dr. Harvey Neidorff, an Active Fellow of the College, arranged the program for this meeting. Dr. H. McLeod Riggins, Assistant Clinical Professor of Medicine, Columbia University College of Physicans and Surgeons, presented a paper on "The Differential Diagnosis of Chronic Pulmonary Disease." Dr. A. Harvey Neidorff, Mercy Hospital, Altoona, spoke on "1954 Methods of Treating Allergic Dermatoses." "The Body Water and Electrolyte" was discussed by Dr. T. S. Danowski, Professor of Research Medicine, University of Pittsburgh School of Medicine; and Dr. Harvey E. Thorpe, Director of Ophthalmology, Montefiore Hospital, Pittsburgh, presented "Ocular Allergy."

OFFICERS ELECTED

The New York Allergy Society has recently elected the following officers: president, Dr. William B. Sherman; president-elect, Dr. Murray Albert; vice president, Dr. Samuel J. Prigel; secretary, Dr. Leoni N. Claman; and treasurer, Dr. Aubrey Whittemore.

RESIDENCY IN ALLERGY

Applications are now being received for a residency in allergy at the Veterans Hospital in Aspinwall, Pennsylvania, and/or at the Montefiore Hospital and Medical Center, University of Pittsburgh, Pittsburgh, Pennsylvania. Please send inquiries to Dr. Leo H. Criep, Bigelow Apartments, Pittsburgh 19, Pennsylvania.

NEWS OF MEMBERS

Dr. Harold S. Tuft, an Active Fellow of the College, formerly of Philadelphia, and Norristown, Pennsylvania, has been appointed fulltime Medical Director of the Jewish National Home for Asthmatic Children at Denver, Colorado. Applications for admission of eligible cases should now be directed to him at 3447 West Nineteenth Avenue, Denver, Colorado.

IMPORTANT NOTICE TO COLLEGE MEMBERS

The remaining members of the College who have not paid their $6.00 assessment toward the American Foundation for Allergic Diseases are urgently requested to help us meet our pledged quota. This assessment is as obligatory as one's dues.

BOOK REVIEWS

THE JEALOUS CHILD. By Edward Podolsky, M.D., Department of Psychiatry, King's County Hospital, Brooklyn, N. Y. 146 pages, including bibliography. Philosophical Library, N. Y., 1954. Price $3.75.

In this volume the author explores the nature of jealousy in children, the factors which nourish the "green-eyed monster," and endeavors to point out to those most concerned with children so addicted what can be done. The emotional, social, and economic conditions are considered. Under each of these categories, specific elements are discussed: chronic ailments, physical deformities, sibling rivalry, adoption, school segregation, illegitimacy, minority groups, et cetera.

All information is presented in broad, general terms and in clear, readable English. Parents, teachers, social workers, and others, concerned with the care of the jealous child, should find it useful.

Dr. Podolsky is a psychiatrist. He has contributed numerous articles to journals devoted to children's problems.—I.W.

PRINCIPLES AND PRACTICE OF ANTIBIOTIC THERAPY. By Henry Welch, Ph.D., Director of the Antibiotics Division, U. S. Food and Drug Administration, Washington, D. C., in collaboration with 16 clinicians and researchers. 699 pages. New York: Medical Encyclopedia, Inc. (Distributed by Blakiston Co.), 1954. Price $12.00.

This volume is a modern clinical encyclopedia on the current available knowledge concerning antibiotics and their use in disease. The first half of the book portrays the history of the evolution of antibiotics and contains a record of the latest experimental and research developments. The second half, written by sixteen outstanding workers, covers the practical and applied uses of antibiotics in various medical specialties. Thus, in one volume we now have the available historical, chemical, pharmacologic, and clinical information concerning the antibiotics and antibiotic therapy, as well as a comprehensive examination of the prophylactic and therapeutic applications of these vital drugs. Experimental work is described, and dosage and vehicles of administration are stressed. The danger of the development of resistant strains is discussed, as are contraindications.

The book is divided into three parts. The first, which is entitled "The Antibiotics," deals with the isolation and development of the antibiotics, with separate chapters on tyrothricin; penicillin; streptomycin and dihydrostreptomycin; bacitracin; polymixin, neomycin, viomycin, subtilin and fumagillin; erythromycin and carbomycin; chlortetracycline; chloramphenicol; oxytetracycline; and tetracycline. Each is discussed from the standpoint of antimicrobial activity, toxicity, absorption and excretion, and dosage forms, with pertinent references to the literature. Part II deals with "Antibiotic Therapy of Infectious Diseases," and various authors discuss the relation of antibiotics to pneumococcal, streptococcal, staphylococcic, meningococcal, and gonococcal infections; treponemal diseases; spirochetal diseases other than the treponematoses; surgical infections; urinary and intestinal tract infections; brucellosis, plague, and tularemia; tuberculosis; virus and rickettsial diseases; and a group of miscellaneous conditions. The third section deals with the "Antibiotic Therapy in Medical Specialties" and covers ophthalmology, pediatrics, oral surgery and dentistry.

This book is more than a revision of "Antibiotic Therapy" by Welch and Lewis; it is a completely new book, which not only brings the former work up to date but broadens the entire field. It should be most helpful to any physician interested in antibiotics.—V.E.S.

MUSIC THERAPY. Edited by Edward Podolsky, M.D., Department of Psychiatry, Kings County Hospital, Brooklyn, N. Y. 335 pages, including bibliography. New York: Philosophical Library, 1954. Price, $6.00.

This volume contains some interesting discussions on the subject of music therapy, the practical applications of music therapy in various mental, emotional, and physical ailments and the effects of music on the mind and emotions, as studied and evaluated by psychiatrists, psychologists, and music therapists within recent years. The papers presented here are from the pens of about thirty-nine different contributors, reprinted from *The American Journal of Psychiatry, Educational Music Magazine, Journal of Nervous and Mental Diseases, Plastic and Reconstructive Surgery, West Virginia Medical Journal,* and others.

While the employment of music for various healing purposes has a long history, it represents a comparatively new field for research. The Introduction relates numerous anecdotes of its use, both traditional and historical, carried down to us from the times of the ancient Hebrews, Confucius, and the Greeks.

The discussions, supplemented by case histories, deal with music and mental health; the past, present, and future of musical therapy; how music produces its effects on the brain and mind; relation of music to diseases of the brain; organization of a music program for rehabilitation of the mentally ill; music as an adjunct to electroshock therapy; music therapy in grief and emotional fatigue and disturbance, tension headache, et cetera. Included, also, is a long paper on music in medicine.—I.W.

EMOTIONAL FACTORS IN SKIN DISEASES. By Eric Wittkower, M.D., Assistant Professor of Psychology, McGill University, and Brian Russell, M.D., Skin Department, The London Hospital. 228 pages. New York: Paul B. Hoeber, Inc., 1953. Price $4.00.

In this unusual book, the first of its kind since 1927, a dermatologist and a psychiatrist collaborate in an attempt to clarify the interrelationship of emotional disturbance and skin disease.

The book consists of two parts: a general section covering such subjects as the development, function, neuroanatomy, and physiology of the skin; the psychosomatic approach to skin diseases; and the investigation and management of patients with skin diseases; and a second part covering skin diseases in which psychosomatic factors are of particular importance, broken down as to abnormal skin sensations and abnormal skin manifestations, and a chapter on the skin and psychoses.

The authors point out in a most enlightening way how the skin stands between the individual's inner and outer worlds, and that a great interplay of forces is reflected in its functioning. From their wide experience they have collected an interesting series of new descriptions of the changes which take place in the skin as a result of emotional and stress-creating situations in daily living.

The extensive experience of the authors and the many case histories included in this volume should make this work helpful in both diagnosis and treatment of skin conditions.—V.E.S.

DERMATOLOGIC FORMULARY. New York Skin and Cancer Unit. By Frances Pascher, M.D., Editor. (Rev. 1953). 149 pages. New York: Paul B. Hoeber, Inc. Price $3.00.

This convenient pocket manual has been prepared by the Skin and Cancer Unit of New York University Hospital and the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, and the prescriptions it contains are the result of fifty years' composite experience in the largest paid outpatient dermatologic service in the world. It contains treatment for all types of skin disorders, including the newest antibiotic ointments, a new and helpful remedy for chronic discoid lupus erythematosus, latest methods for treatment of scabies and pediculosis, and for lepra reactions. It gives the indications, contraindications, and side effects of ACTH, ACTHAR gel, and cortisone; dermatologic indications for banthine and priscoline; procedure for removal of stains from clothing, utensils, and the skin after use of topical remedies; instructions to the pharmacist for prescriptions which are difficult to prepare; sources for substances not generally known; and directions for making palatable unpleasant oral preparations.

It is divided into three sections: Topical Remedies, Systemic Therapy, and Articles for Clinical Use. One hundred and nineteen selected topical remedies are included, covering medicated baths and detergents, medicated soaks and wet dressings, emulsions and oils, shake lotions, magmas, and suspensions, aqueous and alcoholic solutions, lozenges, creams and ointments, pastes, powders and plasters. This section also gives printed instructions which can be issued to patients. The section on Systemic Therapy includes twenty-seven selected prescriptions for oral and parenteral use, including analgesics, antibiotics, antihistamines, hematinics, hormones, sedatives and hypnotics, sulfonamides and sulfones, vitamins, heavy metals, sclerosing solutions, sympathommetic drugs, and biologicals. The third section gives sixteen articles for clinical use, such as cauterizing agents and local anesthetics. A sufficient number of preparations are included to circumvent allergic reactions and idiosyncrasies.

This handy formulary should be a most practical aid to every general practitioner, dermatologist, allergist, and pharmacist.—V.E.S.

FUNDAMENTALS OF OTOLARYNGOLOGY: A Textbook of Ear, Nose and Throat Diseases. By Lawrence R. Boies, M.D., Clinical Professor of Otolaryngology, University of Minnesota Medical School. Second edition. 487 pages, 197 illustrations. Philadelphia: W. B. Saunders Co., 1954. Price $7.00.

This volume is now established as a textbook in many medical schools, and the second edition brings it completely up to date. Two new sections are included: "Introduction to Modern Otolaryngology" and a supplement "The Possibilities of Transudate Disorders in Otolaryngology: Allergy, Autonomic Dysfunction, and Endocrine Imbalance." Information on the new antibiotics is included in the chapter on "Modern Medication of Otolaryngology."

Here the basic principles of otolaryngology are briefly but adequately treated with simplicity and accuracy. The book is designed to give only fundamental information and is not intended to be a complete reference work. References following each chapter point the way to further inquiry. The medical student thus is able to obtain the information necessary to a knowledge of this field, and the practitioner is given the help he needs in managing the ear, nose, and throat problems he encounters in everyday practice.

The book is well illustrated and indexed.—V.E.S.

MEDICAL USES OF CORTISONE INCLUDING HYDROCORTISONE AND CORTICOTROPIN. Edited by Francis D. W. Lukens, M.D., Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. 550 pages, illus. New York: The Blakiston Company, Inc., 1954. Price $7.50.

In the five years since cortisone has been available to physicians, widespread investigations have been made of its action and uses and those of hydrocortisone and corticotropin. As these hormones have been used extensively among the various medical specialties, the reports and studies on their use have been scattered in all types of medical literature. This monograph is written with the intention of bringing together in one volume the results of these studies, together with a compilation of clinical judgment concerning the use of the hormones. Twenty-nine physicians with wide experience in the use of adrenal hormone therapy have contributed to this volume, and each chapter is well documented with references to the literature. In each instance the authors also present their own conclusions concerning the place of the hormones in the various diseases with which they deal.

The book starts with the physiology of the adrenal cortex and the pharmacology of the adrenal cortical hormones and their effects in adrenal insufficiency, and proceeds with the clinical use of cortisone in rheumatoid arthritis and other rheumatic or articular diseases, rheumatic fever, other collagen diseases, asthma and rhinitis, allergic reactions to therapeutic agents, diseases affecting the skin, the granulomas and other pulmonary conditions, infections, eye diseases, gastrointestinal diseases, blood diseases and malignancy, diseases of the kidney, and neuropsychiatric disorders.

The editor expresses the hope that this volume will provide a guide to the constructive use of cortisone and related hormones, and that physicians will apply the same care to their use as they do to digitalis, thyroxin and insulin. This volume is invaluable to the busy physician who makes use of these hormones in his practice, as it provides him with a single volume source of reference material on the subject. It is well indexed.—V.E.S.

PERIPHERAL CIRCULATION IN MAN. Ciba Foundation Symposium. By G. E. Wolstenholme, Jessie S. Freeman, and Joan Etherington, Editors. Boston: Little, Brown and Co., 1954. 219 pages. Price $6.00.

"Peripheral Circulation in Man" was the subject of a symposium held by the Ciba Foundation in London in May, 1953, and the eighteen papers on various aspects of this theme, together with the discussion which followed them, make up this little volume. These papers were presented largely by workers in Great Britain and the United States, although there were also participants from Denmark, Canada, France, and Sweden.

The papers and discussions cover the methods for studying the blood flow, changes in circulation due to exposure to heat or cold, the actions of adrenaline and noradrenaline on blood flow, the neurohistology and reflex control of the circulation and the effects of sympathectomy, the significance of cold agglutinins, and the influence of visceral activity on the peripheral circulation.

The subject of circulation in man is a fruitful field for the collaboration of physiologists, physicians, pathologists, and surgeons, and is one in which the results of clinical work are of great importance to physiologists. The fact that we are still unable to define precisely the laws governing blood flow in vessels and all the factors governing dilatation and constriction points up the need for discussions of this sort.

This volume is brief and simple in its presentations, illustrated with photographs, charts, and tables, and is documented with pertinent references on each subject. It should be of interest to the beginner as well as the expert in the field of peripheral circulation. It is a splendid illustration of the scientific approach to a complex subject.—V.E.S.

YEAR BOOK OF MEDICINE (1953-1954 YEAR BOOK SERIES). Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D., 711 pages, including index. Chicago: The Year Book Publishers, Inc., 1954. Price $6.00.

This compact volume in the Year Book series again gives current diagnostic methods and treatment procedures as gleaned from 525 current international journals from May, 1953 to May, 1954. All through the year the editors have surveyed the tremendous volume of literature and have selected the latest clinical advances which carry the most significance in daily practice. Almost five hundred subjects are covered, 236 diagnostic procedures and 262 new treatment measures.

As before, the book is divided into six sections covering infections; the chest; the blood and blood-forming organs; the heart, blood vessels, and kidneys; the digestive system; and metabolism. Each part is subdivided into a number of sections, with various problems discussed under each, often with a pertinent editorial comment. As throughout the series, ample photographs, charts, and graphs are included.

Coverage of infections has been extensively expanded to include ninety-three articles, and includes several new parts considering antibiotic therapy, diphtheria, chronic bronchitis, shigellosis, bacteroides infection, histoplasmosis, actinomycosis, blastomycosis, syphilis, leptospirosis, amebiasis, toxoplasmosis, rabies, viral meningitis and viral pneumonia, etiology of common respiratory diseases, serum hepatitis, Bornholm disease, vaccinia, hemorrhagic fever, rheumatoid arthritis, sarcoidosis, and anemia in acute infections.

The section on the chest contains new material on congenital disorders and emphysema. Rheumatic heart disease is a new feature discussed under Part IV, and the section on metabolism includes for the first time abnormalities of carbohydrate metabolism; calcium, phosphorus, and the parathyroid glands; and body composition and nutrition.

This treatment of the latest developments in both diagnosis and therapy should be of tremendous value to the general practitioner and specialist in keeping them readily and conveniently informed.—V.E.S.

THE MANUAL OF ANTIBIOTICS. By Henry Welch, Ph.D., Director, Antibiotics Division, U. S. Food and Drug Administration, Washington, D. C. 87 pages. New York: Medical Encyclopedia, Inc., 1954. Price $2.50.

The multiplicity of trade names for antibiotic preparations has increased in the last few years to such proportions that it is all but impossible for the physician, pharmacist, or other worker using these drugs to recall the composition of a product from the trade name. The need for a clarification of this problem is pointed up by the fact that one penicillin preparation has as many as thirty-six trade names.

Dr. Welch, whose wide experience in the field of antibiotics eminently qualifies him to handle such an assignment, has attempted to gather into one volume the names of the currently commercially available antibiotics, their trade names, and their manufacturers. All antibiotics are tabulated alphabetically by their generic names, with their trade names and the names of each manufacturer listed opposite. Along with each of the generic terms are listed the general indications for each drug preparation. Separate indexes list trade names, generic terms, and manufacturers.

By use of this tabulation one can readily identify a trade name and check its generic term, active ingredients, other trade names assigned to the same preparation, and general indications. This ready reference volume should prove a real time saver to those constantly working with antibiotics.—V.E.S.

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IN MEMORIAM

NEWS ITEMS

PROGRESS IN ALLERGY

ANNALS of ALLERGY

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Morrison Hotel
Chicago, Illinois

November-December
1954

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ANNUAL SUBSCRIPTION $7.50 SINGLE COPIES $1.50

Green light for asthma?

not necessarily . . .

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

relief in minutes . . . Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours . . . Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

Prompt and prolonged relief with Tedral can be initiated any time, day or night, whenever needed, without fear of incapacitating side effects.

Tedral provides:

theophylline	2 gr.
ephedrine	3/8 gr.
phenobarbital	1/8 gr.

in boxes of 24, 120 and 1000 tablets

Tedral®

WARNER-CHILCOTT

Quick, lasting

Asthma Relief

without needle or nebulizer

Nephenalin®

Contains aludrine (isopropyl arterenol) HCl 10 mg. in outer coating. Tablet core provides theophylline 125 mg. (2 gr.), ephedrine sulfate 25 mg. (⅜ gr.), phenobarbital 8 mg. (⅛ gr.)

First, put tablet under tongue for immediate relief. *After 5 minutes*, swallow tablet for 4-hour protection. Exceptionally convenient, NEPHENALIN provides *in a single tablet* the answer to the twin problems of immediate relief and prolonged protection.

Bottles of 20 and 100 purple tablets.

Simplified control of

Childhood Asthma

Nephenalin® PEDIATRIC

Contains aludrine (isopropyl arterenol) HCl 5 mg. in outer coating. Tablet core provides theophylline 100 mg. (1½ gr.), ephedrine sulfate 12 mg. (3/16 gr.), phenobarbital 8 mg. (⅛ gr.)

"Gives effective relief in approximately 65% . . ."

"Is relatively free from unpleasant side effects . . ."

". . . no deleterious effects were noted . . ."*

With just one NEPHENALIN PEDIATRIC tablet, held under the tongue for 5 minutes, then swallowed, asthma attacks are relieved promptly and effectively.

Bottles of 20 and 100 square, red tablets.

*Duke University study of 50 children: Dees, S.C., et al., Ann. Allergy, *11*:297, 1953.

Thos. Leeming & Co. Inc. 155 EAST 44TH STREET, NEW YORK 17, N.Y.

Cortef* for inflammation, neomycin for infection:

1. Neo-Cortef* *ointment (topical)*

Each gram contains:

Hydrocortisone acetate ..... 5 mg.
(0.5%) or 10 mg. (1%) or 25 mg. (2.5%)
Neomycin sulfate ..... 5 mg.**
Methylparaben ..... 0.2 mg.
Butyl-p-hydroxybenzoate ..... 1.8 mg.

Supplied:
5 Gm. and 20 Gm. tubes in plastic cases

2. Neo-Cortef* *ophthalmic ointment*

Each gram contains:

Hydrocortisone acetate .. 15 mg. (1.5%)
Neomycin sulfate ..... 5 mg.**

Supplied: 1 drachm applicator tubes

3. Neo-Cortef* *drops (eye and ear)*

Each cc. contains:

Hydrocortisone acetate .. 15 mg. (1.5%)
Neomycin sulfate ..... 5 mg.**

Supplied: 5 cc. dropper bottles

*TRADEMARK
**EQUIVALENT TO 3.5 MG. NEOMYCIN BASE

Upjohn THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

Luzier's Service In The Field Of Allergy

When patient has history of cosmetic sensitivity, or when cosmetics may reasonably be suspected as a contributing if not the etiological factor in your patient's symptoms of allergy, we suggest:

1) Primary tests with those of our products your patient is using or contemplates using, to eliminate products to which there is no demonstrable reaction. (We suggest patch testing because it simulates normal conditions of use. The inside of forearm is good field for these tests.)

2) Secondary tests with constituents of products causing reaction, to trace offending agents. (In specific cases, on written request, we supply testing materials, gratis.)

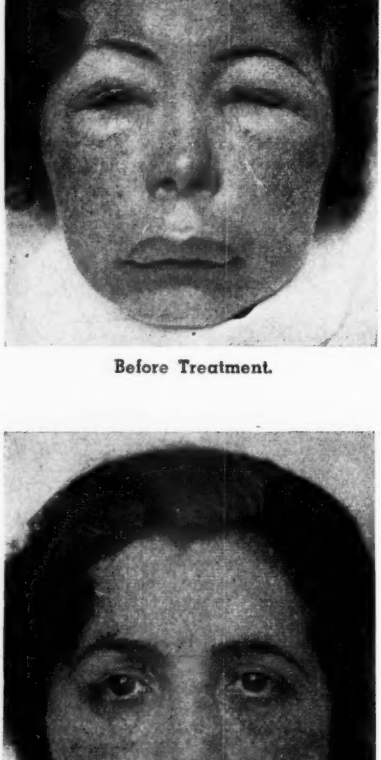
3) Modification of formulae, when possible, to eliminate ingredients to which patient demonstrated a sensitivity. (We extend this service to our patrons without extra charge.)

4) Final check tests with modified formulae to make certain there is no reaction.

Preparations by Luzier are regularly available in an unscented variation. They do not contain orris root or rice starch. Any of their normally harmless constituents, however, is potentially allergenic, for which reason we suggest testing, when practicable. Fees for such tests are patient's responsibility.

LUZIER'S, INC., MAKERS OF FINE COSMETICS . . KANSAS CITY 3, MO.

Angioneurotic Edema Due to Hypersensitiveness to Pork.



Before Treatment.

During and After Treatment with Pork Propeptan.

After only 2 weeks treatment with Pork Propeptan (2 capsules 45 minutes before a meal containing moderate amounts of pork once daily) patient was able to eat pork with no allergic manifestations.

IN THE DIAGNOSIS AND TREATMENT OF NUTRITIONAL ALLERGIES

Faster, more patient-acceptable method of identifiying allergens

Permits the patient to have an **adequate** diet, alleviates existing allergic symptoms promptly, identifies the allergenic food with minimal inconvenience to the patient.

Faster, more patient-acceptable deallergization to the offending foods

Whatever method is used for identification of the allergens.

with specific food

PROPEPTANS

enzyme digests at controlled pH of individual animal and vegetable proteins which retain the specificity of the parent substance without its allergizing effect.

Fifty individual Propeptans are available, covering a wide variety of foods for maximal variation of the diet.

Properly administered, Propeptans first cause partial and temporary "neutralization" of the antibodies. Complete and lasting deallergization then is usually accomplished within 2 or 3 weeks.

Also available: **Polypropeptans,** food digests (Propeptans) of 12 foods, combined for simplification of technique and lower cost, with a more restricted diet.

• *Write for complete descriptive literature, price lists and FREE patient instruction sheets.*

DALARE ASSOCIATES

DALARE ASSOCIATES
2300 Locust Street
Philadelphia 3, Pa.

rapid relief

for coughs from colds or allergies

AMBENYL

TRADE-MARK

AMBENYL owes its special value to the action of *two* outstanding antihistaminics combined with other valuable agents. Benadryl, noted for its antihistaminic-antispasmodic action, and Ambodryl, with its high antihistaminic activity, act together to make coughing patients more comfortable. The antispasmodic, antiallergic, decongestant, and demulcent actions of pleasant-tasting AMBENYL

- quiet the cough reflex
- facilitate expectoration
- decrease bronchospasm
- relieve mucosal congestion

AMBENYL contains in each fluidounce:

Ambodryl hydrochloride (bromodiphenhydramine hydrochloride, Parke-Davis)	24 mg.
Benadryl hydrochloride (diphenhydramine hydrochloride, Parke-Davis)	56 mg.
Dihydrocodeinone bitartrate	⅛ gr.
Ammonium chloride	8 gr.
Potassium guaiacolsulfonate	8 gr.
Menthol	q.s.
Alcohol	5%

Supplied in 16-ounce and 1-gallon bottles.

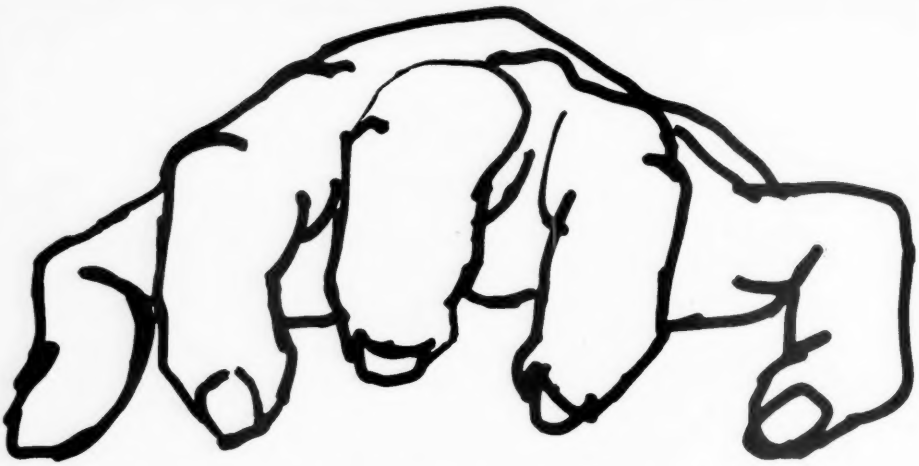
dosage Every three or four hours—adults, 1 to 2 teaspoonfuls; children, ½ to 1 teaspoonful.

MEDICAMENTA VERA

Parke, Davis & Company

DETROIT, MICHIGAN

19458



To control the itching and pain of allergic dermatoses . . .

'Quotane' hydrochloride will safely and effectively stop the itching and pain of most allergic and contact dermatoses.

Quotane's low sensitization index makes it the safest of the topical anesthetics. It is not related chemically to the "-caine" or antihistamine groups, which are powerful sensitizers of the skin.

S.K.F.'s remarkable new topical anesthetic

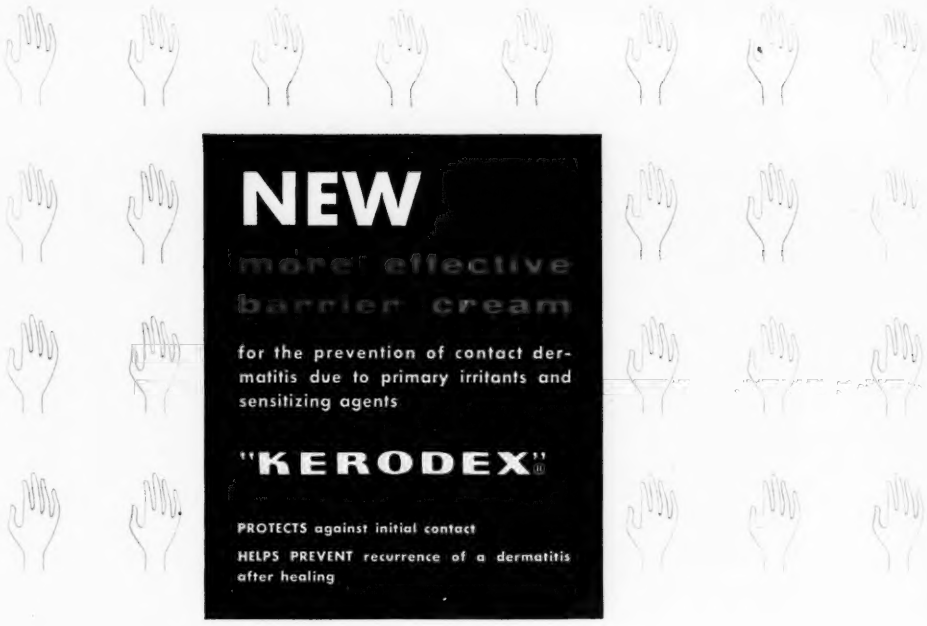
QUOTANE* OINTMENT

unusually safe . . . unusually effective

(Also available: 'Quotane' Lotion—when a drying effect is desired.)

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for dimethisoquin hydrochloride, S.K.F.



"KERODEX" provides a protective coating . . . invisible, yet strong . . . as elastic as the skin itself. "Kerodex" is recommended for the prevention of housewives' eczema, "dishpan hands," chafing and diaper rash, inflammation due to body fluids and discharges. A vast range of occupational dermatoses may also be prevented with **"KERODEX"**.

2 TYPES AVAILABLE

"KERODEX" No. 71 (water-repellent) for wet work protects against soaps, shampoos, bleaching and washing compounds, fruit and vegetable juices, drugs in water solution, acids, alkalis, etc.

"KERODEX" No. 51 (water-miscible) for dry work protects against dust, grime, garden soil, solvents, paints, cleaning fluids, oils, grease, etc.

Each type is supplied in 4 oz. tubes and 1 lb. containers.

Literature available on request

- nonirritating and nonsensitizing
- may be used with equal safety on the face, hands, or any other area of the skin
- keeps pores and follicles free from foreign matter
- easy to use—economical—esthetically acceptable

Ayerst NEW YORK, N. Y. MONTREAL, CANADA

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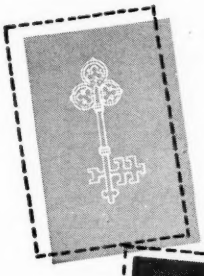
Index to Advertisers

There are no products which are used by allergists equal or superior to those of our advertisers. Please patronize them first.

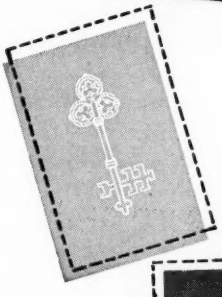
Since its inception, the ANNALS OF ALLERGY has had a policy whereby only advertisements approved by the American Medical Association, or which have not been rejected by them, are accepted. This keeps the standards of the ANNALS the highest of any journal of its kind.

KEY to cough control . . .



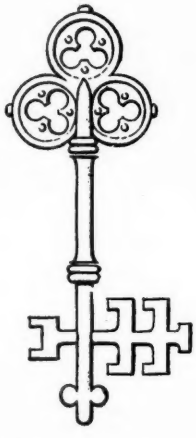
Topical anesthetic action
more powerful than
that of cocaine

Antihistaminic action
which helps control cough,
bronchial spasm, and
allergy-caused congestion



Sedative action
which may make "cough patients"
less irritable in general

Expectorant action
to aid in secretion of
protective mucus, thus
rendering the cough productive



PHENERGAN®
PROMETHAZINE

Expectorant with Codeine
Expectorant Plain (without Codeine)
Bottles of 1 pint

Wyeth®
Philadelphia 2, Pa.

Vaporizer for the Highest Output of Steam per hour

FOR YOUR FILES:
FACTS ABOUT THE
DEVILBISS VAPORIZER NO. 149

By all standards of judgment, the finest vaporizer you can recommend to your patients is the DeVilbiss No. 149. Of particular importance is the fact that the DeVilbiss No. 149 *converts 8 to 10 ozs. of water into vapor each hour.*

Has automatic safety shut-off. Operates 8 to 10 hours without refilling. Vaporizer bears the seal of the Underwriters' Laboratories and the Good Housekeeping Seal of Approval. Easy to care for and covered by complete service policy. You can recommend the DeVilbiss Vaporizer No. 149 to your patients with complete confidence. $15.00. The DeVilbiss Company, Somerset, Pa., and Barrie, Ontario.

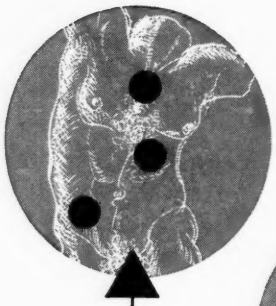
DEVILBISS

SOMERSET, PA.

ATOMIZERS · VAPORIZERS · NEBULIZERS

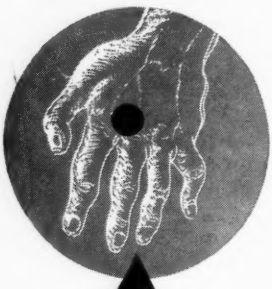
★

"The Line the Physician Knows and Prescribes"



ALLERGIC MANIFESTATIONS

DERMATOSES



OPHTHALMIC DISORDERS

Piromen®

(PSEUDOMONAS POLYSACCHARIDE) is proving effective in the control of a wide variety of allergies, dermatoses, and certain ophthalmic disorders. When injected, it produces a leucocytosis and initiates generalized activation of the reticulo-endothelial system. Supplied in 10 cc. vials containing either 4 or 10 gamma (micrograms) per cc., *Piromen* may be used safely within a wide dosage range.

For a comprehensive booklet detailing the use of this effective therapeutic agent, merely write "Piromen" on your Rx, and mail to—

Manufactured by **TRAVENOL LABORATORIES, INC.**

a subsidiary of BAXTER LABORATORIES, INC., MORTON GROVE, ILLINOIS